

**Coeliac disease: recognition and  
assessment of coeliac disease**

**Appendices vol 1**

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## **Contents**

- 6.1 Scope
- 6.2 Key Clinical Questions & Protocols
- 6.3 ROC Curves & Forest Plots
- 6.4 Search Strategies
- 6.5 Health Economics Evidence & Evidence Tables
- 6.6 Evidence Tables (available as a separate document, appendices vol 2)

## ***Appendix 6.1 Scope***

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

### **SCOPE**

#### **1 Guideline title**

Coeliac disease: recognition and assessment of coeliac disease

##### **1.1 Short title**

Coeliac disease

#### **2 Background**

- a) The Department of Health has asked the National Institute for Health and Clinical Excellence (NICE) to develop a clinical guideline on the recognition and diagnosis of coeliac disease for use in the NHS in England and Wales. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.
- b) The Institute's clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued have the effect of updating the Framework.
- c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their

individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

### **3 Clinical need for the guideline**

- a) Coeliac disease is an autoimmune condition associated with chronic inflammation of the small intestine, which can lead to malabsorption of nutrients. Dietary proteins, known as glutes, that are present in wheat, barley and rye activate an abnormal mucosal immune response. Clinical and histological improvements usually follow the withdrawal of gluten from the diet.
- b) Coeliac disease can present with a wide range of clinical features, both gastrointestinal (such as indigestion, diarrhoea, abdominal pain, bloating, distension or constipation) and non-gastrointestinal (such as fatigue, dermatitis herpetiformis, iron deficiency, anaemia, osteoporosis, reproductive problems, short stature, neuropathy, ataxia or delayed puberty). Although some patients present with typical symptoms, others have few or no symptoms. Also symptoms may be mis-diagnosed as other conditions, notably irritable bowel syndrome (IBS).
- c) The prevalence of coeliac disease has been calculated from population screening studies, which suggest that 1 out of every 100 people in Europe is affected, and under-diagnosis is a continuing concern. The complications of coeliac disease (which may be present at diagnosis) can include osteoporosis, ulcerative jejunitis, sepsis and intestinal lymphoma.
- d) People with autoimmune conditions such as type 1 diabetes and autoimmune thyroid disease, or those with a first-degree family

history of coeliac disease, have an increased likelihood of coeliac disease.

- e) There is evidence that coeliac disease is underdiagnosed when it presents in primary care and other non-specialist settings. There is also uncertainty regarding which are the most appropriate serological and other immunological tests to use. Serological tests have an important role in establishing a diagnosis and identifying people who should be referred to specialist gastroenterology services for endoscopic biopsy. Therefore there is a need to determine how to identify and assess people with symptoms and/or signs suggestive of coeliac disease, the precise role of serological testing, and who should be referred for endoscopic biopsy.
- f) The availability of self-diagnosis kits has increased, and healthcare professionals need to be aware of how these are being used and how their use may affect testing strategy.

## **4 The guideline**

- a) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider.
- b) The areas that will be addressed by the guideline are described in the following sections.

### **4.1 Population**

#### **4.1.1 Groups that will be covered**

- a) Adults and children with symptoms and/or signs suggestive of coeliac disease.
- b) Specific subgroups in whom coeliac disease is known to be more prevalent than in the general population:

- people with coexisting conditions such as type 1 diabetes, Down's syndrome, thyroid conditions
- first-degree relatives of people with coeliac disease.

#### **4.1.2 Groups that will not be covered**

- a) People with other gastrointestinal disorders.

#### **4.2 *Healthcare setting***

Primary and secondary care.

#### **4.3 *Clinical management***

##### **4.3.1 Areas that will be covered**

- a) Recognition, assessment and investigation of people with presenting symptoms and/or signs, either gastrointestinal or non-gastrointestinal, that are suggestive of coeliac disease, including:
- presenting features, history (including family history) and examination
  - purpose, timing, accuracy and diagnostic value of the serological tests, this will include:
    - IgA-tTG (immunoglobulin A-tissue transglutaminase antibody)
    - IgG-tTG (immunoglobulin G-tissue transglutaminase antibody)
    - IgA-EMA (immunoglobulin A-endomysial antibody)
    - IgG-EMA (immunoglobulin G-endomysial antibody)
    - IgA-AGA and IgG-AGA (immunoglobulin A- and immunoglobulin G-antigliadin antibody)
  - purpose, timing, accuracy and diagnostic value of the human leukocyte antigen (HLA) DQ2 and DQ8 immunological test

- appropriate use and frequency of repeat serological testing
  - testing for IgA deficiency.
- b) Where there is evidence, the guideline will consider any subgroups in whom the recognition and diagnosis of coeliac disease may differ from the general population.
- c) Indications for referral for endoscopic biopsy.
- d) Information and support for patients and their families or carers, including information before testing and referral.

#### **4.3.2 Areas that will not be covered**

- a) Diagnosis of coeliac disease using endoscopic biopsy.
- b) Management of coeliac disease.
- c) Population-based screening for coeliac disease.
- d) Accuracy and use of self-diagnosis kits.

#### **4.4 Key outcome measures**

- a) Diagnostic accuracy.
- b) Morbidity and mortality (including morbidity related to long term delay in diagnosis).
- c) Adverse events.
- d) Health-related quality of life.

#### **4.5 Economic aspects**

In line with 'The guidelines manual', developers will take into account both clinical and cost effectiveness. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit

of effectiveness is the quality-adjusted life year (QALY), and costs in the 'reference case' will be from an NHS and Personal Social Services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual'.

## **4.6 Status**

### **4.6.1 Scope**

This is the final scope.

#### **Related NICE guidance**

Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. NICE clinical guideline 61 (2008). Available from [www.nice.org.uk/CG061](http://www.nice.org.uk/CG061)

Chronic fatigue syndrome/myalgic encephalomyelitis; diagnosis and management. NICE clinical guideline 53 (2007). Available from [www.nice.org.uk/CG053](http://www.nice.org.uk/CG053)

type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. NICE clinical guideline 15 (2004). Available from [www.nice.org.uk/CG015](http://www.nice.org.uk/CG015)

#### **4.6.2 Guideline**

The development of the guideline recommendations will begin in August 2008.

### **5 Further information**

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'
- 'The guide to the short clinical guideline process'.

These are available from the NICE website

([www.nice.org.uk/guidelinesmanual](http://www.nice.org.uk/guidelinesmanual)). Information on the progress of the guideline will also be available from the website.

## **Scope Appendix A: Structured clinical questions**

### **Questions on presentation and diagnosis**

- Identification of the presenting features of coeliac disease, including:
  - gastrointestinal features (for example, abdominal bloating, diarrhoea)
  - non-gastrointestinal features (for example, anaemia, osteoporosis)
  - whether presentation differs in specified subgroups such as ethnic groups, sex and groups with co-existing conditions (such as type 1 diabetes, Down's syndrome, and autoimmune thyroiditis)
  - the long-term effects of non-diagnosed coeliac disease.
- the efficacy of serological tests (IgA–tTG, IgG–tTG, IgA–EMA, IgG–EMA, IgA–AGA and IgG–AGA) and immunological tests (HLA) DQ2 and DQ8 for diagnosing coeliac disease (using a reference standard of endoscopic biopsy)
  - when to offer testing
  - whether efficacy varies across specified subgroups
  - whether efficacy differs between symptomatic and non-symptomatic (silent) coeliac disease
  - sequencing and number of tests
  - value of testing in patients without symptoms.

### **Question on referral**

- Identifying which test results indicate a need for referral, specifically for intestinal biopsy.

### **Question on information needs of patients**

- Information needs of patients and carers, particularly before testing is initiated.

## **Scope Appendix B: Referral from the Department of Health**

The Department of Health asked NICE:

'To prepare a clinical guideline on the recognition and assessment of coeliac disease.'

## **Appendix 6.2 Key Clinical Questions & Protocols**

### **Key Clinical questions**

What is the incidence rate of coeliac disease, nationally and internationally?

Are there certain ethnic groups where coeliac disease is more prevalent? Is there any difference in the occurrence of coeliac disease between males and females? What is the risk of coeliac disease in first-degree relatives of those with coeliac disease?

What are the signs and symptoms which indicate a diagnosis of coeliac disease, both gastrointestinal and non-gastrointestinal?

Which co-existing conditions are associated with an increased risk of coeliac disease?

What information do patients need firstly to decide whether to undergo serological testing, and if being tested do patients need to ensure that test results are as accurate as possible?

What is the sensitivity and specificity of the serological tests for coeliac disease? Are these sensitivity/specificity results different in any specified subgroups?

Which serological test is the appropriate first option for coeliac disease? Depending on test results, should more than one test be used and if so what is the sequence of testing for coeliac disease? Following which sequence of tests and test results is it appropriate to refer onwards for intestinal biopsy?

What are the possible long-term consequences of undiagnosed coeliac disease?

### **Review Protocol**

	<b>Details</b>	<b>Additional comments</b>	<b>Status</b>
Review question ID	1 & 2 (background questions)	...	...

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Review question	<i>What is the incidence rate of coeliac disease, nationally and internationally?</i>  <i>Are there groups in which coeliac disease is more prevalent: - ethnic groups, first-degree relatives?</i>	...	
Objectives	<i>To identify the incidence of coeliac disease, a condition which is reported as a poorly recognised condition which is therefore under-diagnosed</i>	...	As per protocol
Language	<i>English</i>	...	As per protocol
Study design	<i>Large, European-based population-based studies, screening studies, systematic reviews</i>	...	As per protocol
Status	<i>Published papers</i>	...	As per protocol
Population	<i>Adults and children who are being investigated for coeliac disease.</i>  <i>Studies which include large, population-based assessment of the incidence of coeliac disease. Large studies which consider in the incidence of coeliac disease in specified subgroups</i>	...	As per protocol
Outcomes	<i>Incidence rate of coeliac disease determined by diagnosis using recognised tests</i>	...	As per protocol
Other criteria for inclusion/exclusion of studies	<u><i>Inclusion:</i></u> <i>Studies using recognised diagnostic processes</i>  <u><i>Exclusion:</i></u> <i>Small, locally based studies, coeliac disease diagnosed not using intestinal biopsy (reference standard)</i>		As per protocol
Search strategies	...	...	As per protocol
Review strategies	<i>Studies will be assessed for study quality as per NICE guidelines manual and SCG process</i>  <i>Evidence table and narrative summary will be used to summarise the evidence.</i>	As a background question the search strategy will be agreed with the IS	

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	<b>Details</b>	<b>Additional comments</b>	<b>Status</b>
Review question ID	3	...	...
Review question	<i>What are the signs and symptoms which indicate a diagnosis of coeliac disease?</i> - <i>gastrointestinal symptoms</i> - <i>non-gastrointestinal symptoms</i>	Possible GI signs and symptoms: diarrhoea, constipation, abdominal bloating, abdominal pain/cramping, flatulence  Possible non-GI signs and symptoms: iron-deficiency anaemia, epilepsy and other neurological conditions, osteoporosis, unexplained fertility, delayed puberty, short stature, headaches, general lethargy/tired all the time/fatigue	
Objectives	<i>To identify presenting signs and symptoms which indicate a diagnosis of coeliac disease.</i> <i>To identify if there are gastrointestinal presenting signs and symptoms which are not associated with a possible diagnosis of coeliac disease</i>	...	As per protocol
Language	<i>English</i>	...	As per protocol
Study design	<i>Diagnostic studies, case-control, cohort, systematic reviews</i>	...	As per protocol
Status	<i>Published papers</i>	...	As per protocol
Population	<i>Adults and children who are being investigated for coeliac disease</i>	...	As per protocol
Outcomes	<i>Gastrointestinal symptoms associated and/or not associated with a diagnosis of coeliac disease</i> <i>Non-gastrointestinal symptoms associated with a diagnosis of coeliac disease</i>	...	As per protocol
Other criteria for inclusion/exclusion of studies	<u><i>Exclusion:</i></u> <i>Case study or case series papers</i>		As per protocol
Search strategies	...	Possible cross-referral/use of IBS search strategy	As per protocol

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Review strategies	<p><i>Studies will be assessed for study quality as per NICE guidelines manual and SCG process</i></p> <p><i>Evidence table and narrative summary will be used to summarise the evidence.</i></p>	...	
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	<b>Details</b>	<b>Additional comments</b>	<b>Status</b>
Review question ID	4	...	...
Review question	<i>Which co-existing conditions are associated with an increased risk of coeliac disease?</i>	...	
Objectives	<i>To identify if and which co-existing conditions are associated with a higher rate of coeliac disease (need to consider if certain conditions need to be regarded as possible signs/symptoms for coeliac disease)</i>	Possible: auto-immune conditions, type 1 diabetes, thyroiditis, atopy, alopecia, rheumatoid arthritis, liver disease/abnormal liver function,	As per protocol
Language	<i>English</i>	...	As per protocol
Study design	<i>Cohort studies, large population-based screening studies, systematic reviews</i>	...	As per protocol
Status	<i>Published papers</i>	...	As per protocol
Population	<i>Adults and children who are being investigated for coeliac disease</i>	...	As per protocol
Outcomes	<i>Identification of co-existing conditions which are associated with an increased risk of coeliac disease</i>	...	As per protocol
Other criteria for inclusion/exclusion of studies	<u>Exclusion:</u> <i>Case study or case series papers</i>		As per protocol
Search strategies	...	...	As per protocol
Review strategies	<p><i>Studies will be assessed for study quality as per NICE guidelines manual and SCG process</i></p> <p><i>Evidence table and narrative summary will be used to summarise the evidence.</i></p>	...	

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	<b>Details</b>	<b>Additional comments</b>	<b>Status</b>
Review question ID	5	...	...
Review question	<i>What information do patients or patients and carers need to decide whether to undergo serological testing?</i>	...	
Objectives	<i>To identify the information needed to ensure that patients can make an informed choice about having serological testing for coeliac disease.</i>	Patients need to continue taking a coeliac-containing diet prior to having the serological tests	As per protocol
Language	<i>English</i>	...	As per protocol
Study design	<i>Qualitative studies, survey studies, expert opinion</i>	...	As per protocol
Status	<i>Published papers</i>	...	As per protocol
Population	<i>Adults and children who are being investigated for coeliac disease</i>	...	As per protocol
Outcomes		...	As per protocol
Other criteria for inclusion/ exclusion of studies	<u><i>Exclusion:</i></u> <i>Case study or case series papers</i>		As per protocol
Search strategies	...	Search strategy will need to be focused as there will be a lot of information relating to the information of those with diagnosed coeliac disease and gluten-free diets	As per protocol
Review strategies	<i>Studies will be assessed for study quality as per NICE guidelines manual and SCG process</i>  <i>Evidence table and narrative summary will be used to summarise the evidence.</i>	...	

	<b>Details</b>	<b>Additional comments</b>	<b>Status</b>
Review question ID	6 & 7	...	...
Review question	<i>What is the sensitivity and specificity of the serological tests for</i>	Comparison with other	

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	<p><i>coeliac disease? Are these sensitivity/specificity results different in any specified subgroups? Is there any evidence regarding patients on different diets, specifically relating to the effect of the amount of gluten being eaten and the effect on test efficacy?</i></p> <p><i>Which serological test is the appropriate first option for coeliac disease? Depending on test results, should more than one test be used and if so what is the sequence of testing for coeliac disease? Following which sequence of tests and test results is it appropriate to refer onwards for intestinal biopsy?</i></p>	<p>serological tests and intestinal biopsy (reference standard)</p> <p>Identification of when it is appropriate to do further serological tests (sequencing) and when it is appropriate to refer for intestinal biopsy</p>	
Objectives		...	As per protocol
Language	<i>English</i>	...	As per protocol
Study design	<i>Diagnostic studies, RCTs, systematic reviews, expert opinion</i>	...	As per protocol
Status	<i>Published papers</i>	...	As per protocol
Population	<i>Adults and children who are being investigated for coeliac disease</i>	...	As per protocol
Outcomes	<i>Measures of diagnostic tests</i>	...	As per protocol
Other criteria for inclusion/exclusion of studies	<p><u><i>Inclusion:</i></u> <i>Studies which include the specified serological tests</i></p> <p><u><i>Exclusion:</i></u> <i>Studies with no comparator groups</i></p>		As per protocol
Search strategies	...	...	As per protocol
Review strategies	<p><i>Studies will be assessed for study quality as per NICE guidelines manual and SCG process</i></p> <p><i>Evidence table and narrative summary will be used to summarise the evidence (summary ROC curves/meta-analysis may be used).</i></p>	...	

	<b>Details</b>	<b>Additional comments</b>	<b>Status</b>
Review question ID	8	...	...

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Review question	<i>What are the possible long-term consequences of undiagnosed coeliac disease?</i>	...	
Objectives		...	As per protocol
Language	<i>English</i>	...	As per protocol
Study design	<i>Longitudinal studies, cohort studies, systematic reviews, expert opinion</i>	...	As per protocol
Status	<i>Published papers</i>	...	As per protocol
Population	<i>Adults and children who are being investigated for coeliac disease</i>	...	As per protocol
Outcomes		...	As per protocol
Other criteria for inclusion/ exclusion of studies	<u>Exclusion:</u> <i>Case study or case series papers</i>		As per protocol
Search strategies	...	...	As per protocol
Review strategies	<i>Studies will be assessed for study quality as per NICE guidelines manual and SCG process</i>  <i>Evidence table and narrative summary will be used to summarise the evidence.</i>	...	

## Appendix 6.3 ROC Curves & Forest Plots

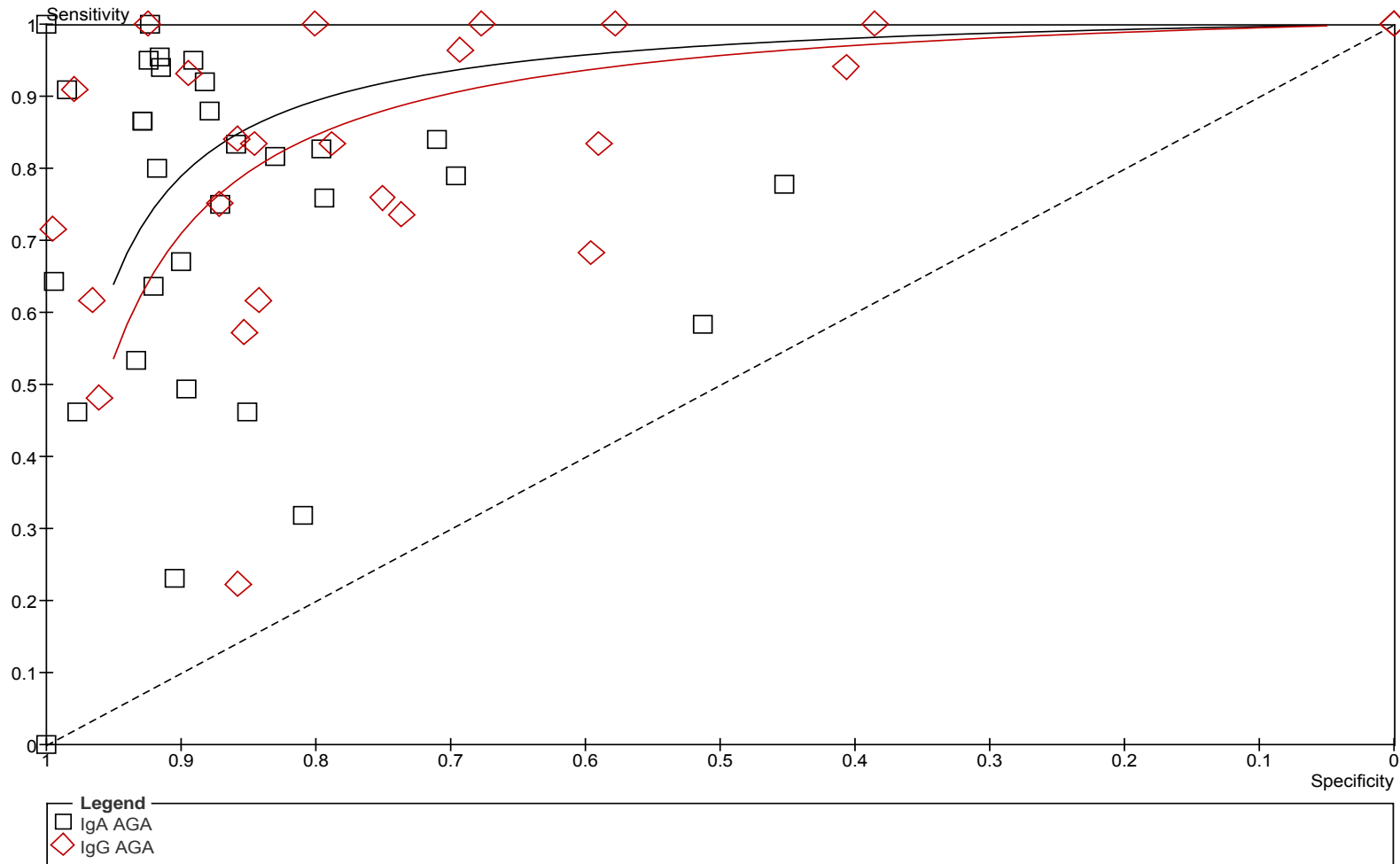
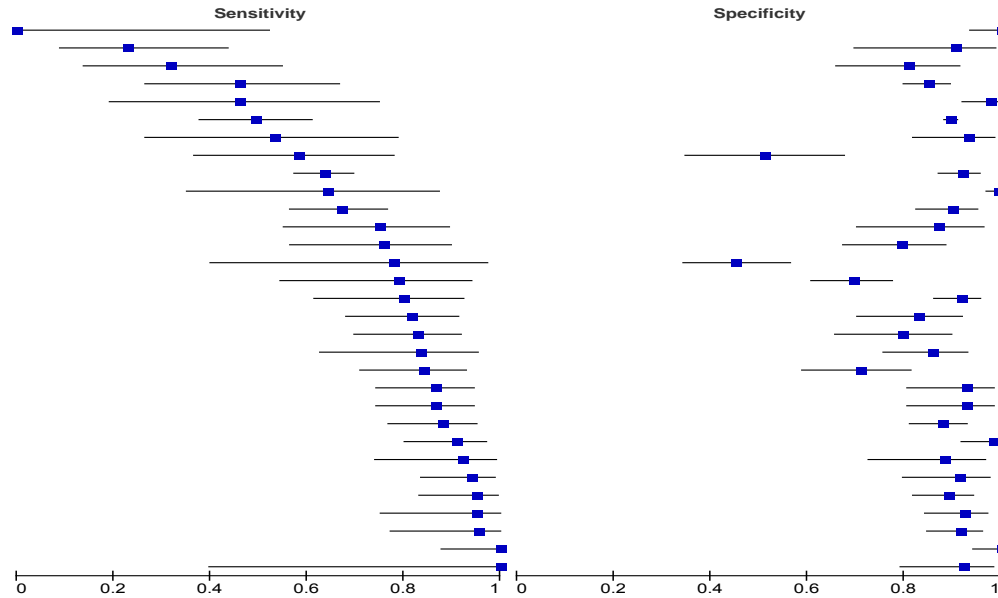


Figure 1: IgA/IgG anti gliadin antibodies

IgA AGA

Study	TP	FP	FN	TN	Sensitivity	Specificity
Meini 1996	0	0	5	55	0.00 [0.00, 0.52]	1.00 [0.94, 1.00]
Altuntas 1998	6	2	20	19	0.23 [0.09, 0.44]	0.90 [0.70, 0.99]
Viola 2004	7	8	15	34	0.32 [0.14, 0.55]	0.81 [0.66, 0.91]
Reeves 2006	12	34	14	194	0.46 [0.27, 0.67]	0.85 [0.80, 0.89]
Bode 1994	6	2	7	85	0.46 [0.19, 0.75]	0.98 [0.92, 1.00]
Hopper 2008	38	200	39	1723	0.49 [0.38, 0.61]	0.90 [0.88, 0.91]
Rich 1990	8	3	7	42	0.53 [0.27, 0.79]	0.93 [0.82, 0.99]
Artan 1998	14	19	10	20	0.58 [0.37, 0.78]	0.51 [0.35, 0.68]
Tesei 2003	159	14	91	162	0.64 [0.57, 0.70]	0.92 [0.87, 0.96]
Bode 1993	9	1	5	175	0.64 [0.35, 0.87]	0.99 [0.97, 1.00]
Carroccio 2002	61	10	30	90	0.67 [0.56, 0.77]	0.90 [0.82, 0.95]
Chirido 1999	21	4	7	27	0.75 [0.55, 0.89]	0.87 [0.70, 0.96]
Johnston 2003	22	13	7	50	0.76 [0.56, 0.90]	0.79 [0.67, 0.89]
Kaukinen 2000	7	46	2	38	0.78 [0.40, 0.97]	0.45 [0.34, 0.56]
Valdimarsson 1996	15	38	4	87	0.79 [0.54, 0.94]	0.70 [0.61, 0.78]
Chartrand 1997	24	12	6	134	0.80 [0.61, 0.92]	0.92 [0.86, 0.96]
Vogelsang 1995	40	9	9	44	0.82 [0.68, 0.91]	0.83 [0.70, 0.92]
Wolters 2002	43	10	9	39	0.83 [0.70, 0.92]	0.80 [0.66, 0.90]
Russo 1999	20	10	4	61	0.83 [0.63, 0.95]	0.86 [0.76, 0.93]
Kocna 2002	42	20	8	49	0.84 [0.71, 0.93]	0.71 [0.59, 0.81]
Lindquist 1993	45	3	7	39	0.87 [0.74, 0.94]	0.93 [0.81, 0.99]
Maki 1991	45	3	7	39	0.87 [0.74, 0.94]	0.93 [0.81, 0.99]
Lindberg 1985	51	16	7	116	0.88 [0.77, 0.95]	0.88 [0.81, 0.93]
Ascher 1996	50	1	5	64	0.91 [0.80, 0.97]	0.98 [0.92, 1.00]
Goncz 1991a	23	4	2	30	0.92 [0.74, 0.99]	0.88 [0.73, 0.97]
Poddar 2002	47	4	3	43	0.94 [0.83, 0.99]	0.91 [0.80, 0.98]
Bardella 2001	38	12	2	98	0.95 [0.83, 0.99]	0.89 [0.82, 0.94]
Goncz 1991	19	6	1	73	0.95 [0.75, 1.00]	0.92 [0.84, 0.97]
Bahia 2001	21	9	1	98	0.95 [0.77, 1.00]	0.92 [0.85, 0.96]
McMillan 1991	28	0	0	61	1.00 [0.88, 1.00]	1.00 [0.94, 1.00]
Del Rosario 1998	4	3	0	36	1.00 [0.40, 1.00]	0.92 [0.79, 0.98]



IgG AGA

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaukinen 2000	2	12	7	72	0.22 [0.03, 0.60]	0.86 [0.76, 0.92]
Hopper 2008	37	77	40	1849	0.48 [0.37, 0.60]	0.96 [0.95, 0.97]
McMillan 1991	16	9	12	52	0.57 [0.37, 0.76]	0.85 [0.74, 0.93]
Reeves 2006	16	36	10	192	0.62 [0.41, 0.80]	0.84 [0.79, 0.89]
Bode 1994	8	3	5	84	0.62 [0.32, 0.86]	0.97 [0.90, 0.99]
Viola 2004	15	17	7	25	0.68 [0.45, 0.86]	0.60 [0.43, 0.74]
Bode 1993	10	1	4	175	0.71 [0.42, 0.92]	0.99 [0.97, 1.00]
Vogelsang 1995	36	14	13	39	0.73 [0.59, 0.85]	0.74 [0.60, 0.85]
Chirido 1999	21	4	7	27	0.75 [0.55, 0.89]	0.87 [0.70, 0.96]
Carroccio 2002	69	25	22	75	0.76 [0.66, 0.84]	0.75 [0.65, 0.83]
Russo 1999	20	11	4	60	0.83 [0.63, 0.95]	0.85 [0.74, 0.92]
Chartrand 1997	25	31	5	115	0.83 [0.65, 0.94]	0.79 [0.71, 0.85]
Artan 1998	20	16	4	23	0.83 [0.63, 0.95]	0.59 [0.42, 0.74]
Tesei 2003	210	25	40	151	0.84 [0.79, 0.88]	0.86 [0.80, 0.91]
Bahia 2001	20	1	2	45	0.91 [0.71, 0.99]	0.98 [0.88, 1.00]
Lindberg 1985	54	14	4	118	0.93 [0.83, 0.98]	0.89 [0.83, 0.94]
Kocna 2002	47	41	3	28	0.94 [0.83, 0.99]	0.41 [0.29, 0.53]
Ascher 1996	53	20	2	45	0.96 [0.87, 1.00]	0.69 [0.57, 0.80]
Goncz 1991	20	6	0	73	1.00 [0.83, 1.00]	0.92 [0.84, 0.97]
Del Rosario 1998	4	24	0	15	1.00 [0.40, 1.00]	0.38 [0.23, 0.55]
Wolters 2002	43	7	0	0	1.00 [0.92, 1.00]	0.00 [0.00, 0.41]
Altuntas 1998	26	21	0	0	1.00 [0.87, 1.00]	0.00 [0.00, 0.16]
Meini 1996	5	11	0	44	1.00 [0.48, 1.00]	0.80 [0.67, 0.90]
Goncz 1991a	25	11	0	23	1.00 [0.86, 1.00]	0.68 [0.49, 0.83]
Rich 1990	15	19	0	26	1.00 [0.78, 1.00]	0.58 [0.42, 0.72]

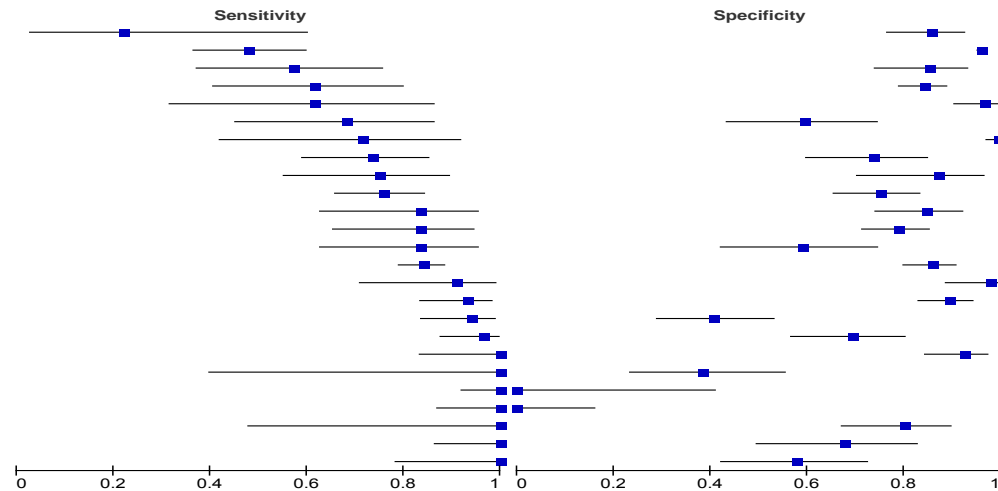
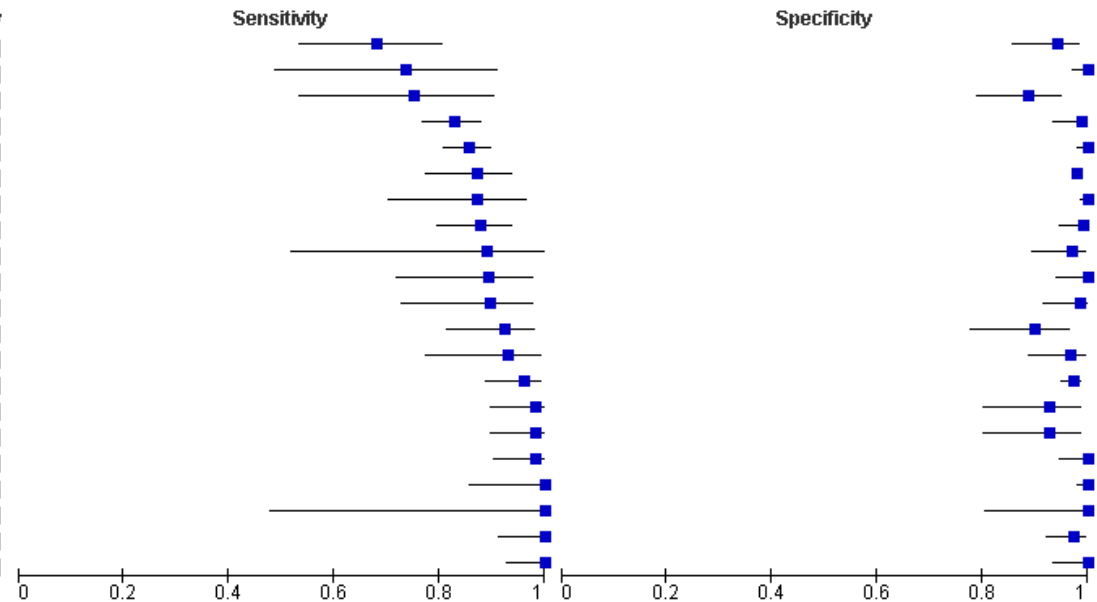


Figure 2: IgA/IgG anti gliadin antibodies

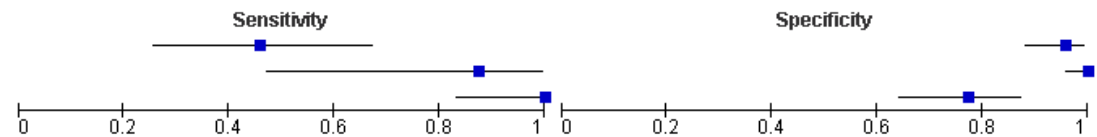
**IgA EMA ME**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kocna 2002	34	4	16	65	0.68 [0.53, 0.80]	0.94 [0.86, 0.98]
Valdimarsson 1996	14	0	5	125	0.74 [0.49, 0.91]	1.00 [0.97, 1.00]
Russo 1999	18	8	6	63	0.75 [0.53, 0.90]	0.89 [0.79, 0.95]
Carroccio 2006	159	1	33	81	0.83 [0.77, 0.88]	0.99 [0.93, 1.00]
Tesei 2003	214	0	36	176	0.86 [0.81, 0.90]	1.00 [0.98, 1.00]
Hopper 2008	67	37	10	1886	0.87 [0.77, 0.94]	0.98 [0.97, 0.99]
Dickey 1997	27	0	4	287	0.87 [0.70, 0.96]	1.00 [0.99, 1.00]
Carroccio 2002	80	1	11	99	0.88 [0.79, 0.94]	0.99 [0.95, 1.00]
Chan 2001	8	2	1	64	0.89 [0.52, 1.00]	0.97 [0.89, 1.00]
McMillan 1991	25	0	3	61	0.89 [0.72, 0.98]	1.00 [0.94, 1.00]
Johnston 2003	26	1	3	62	0.90 [0.73, 0.98]	0.98 [0.91, 1.00]
Wolters 2002	48	5	4	44	0.92 [0.81, 0.98]	0.90 [0.78, 0.97]
Viola 2004	27	2	2	60	0.93 [0.77, 0.99]	0.97 [0.89, 1.00]
Kumar 1989	73	11	3	376	0.96 [0.89, 0.99]	0.97 [0.95, 0.99]
Maki 1991	51	3	1	38	0.98 [0.90, 1.00]	0.93 [0.80, 0.98]
Lindquist 1993	51	3	1	38	0.98 [0.90, 1.00]	0.93 [0.80, 0.98]
Ascher 1996	54	0	1	65	0.98 [0.90, 1.00]	1.00 [0.94, 1.00]
Carroccio 2002a	24	0	0	183	1.00 [0.86, 1.00]	1.00 [0.98, 1.00]
Del Rosario 1998	5	0	0	17	1.00 [0.48, 1.00]	1.00 [0.80, 1.00]
Bardella 2001	40	3	0	107	1.00 [0.91, 1.00]	0.97 [0.92, 0.99]
Vogelsang 1995	49	0	0	53	1.00 [0.93, 1.00]	1.00 [0.93, 1.00]



**IgA EMA HU**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Russo 1999	11	3	13	68	0.46 [0.26, 0.67]	0.96 [0.88, 0.99]
Kaukinen 2000	7	0	1	84	0.88 [0.47, 1.00]	1.00 [0.96, 1.00]
Iltanen 1999	20	13	0	44	1.00 [0.83, 1.00]	0.77 [0.64, 0.87]



**IgG EMA ME**

Study	TP	FP	FN	TN	Sensitivity	Specificity
McMillan 1991	11	1	17	60	0.39 [0.22, 0.59]	0.98 [0.91, 1.00]

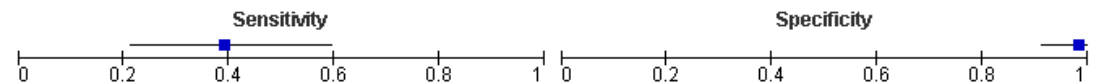
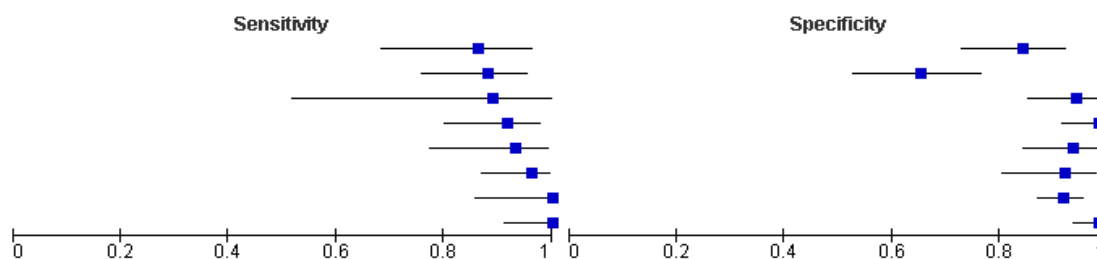


Figure 3: IgA/IgG anti endomysial antibodies (ME, monkey oesophagus; HU, human umbilical cord)

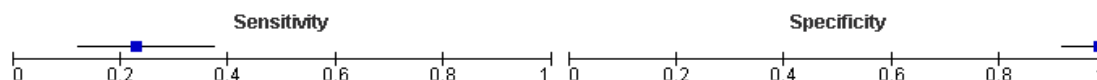
**IgA tTG GP**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Johnston 2003	25	10	4	53	0.86 [0.68, 0.96]	0.84 [0.73, 0.92]
Kocna 2002	44	24	6	45	0.88 [0.76, 0.95]	0.65 [0.53, 0.76]
Chan 2001	8	4	1	62	0.89 [0.52, 1.00]	0.94 [0.85, 0.98]
Troncone 1999	44	1	4	62	0.92 [0.80, 0.98]	0.98 [0.91, 1.00]
Viola 2004	27	4	2	58	0.93 [0.77, 0.99]	0.94 [0.84, 0.98]
Wolters 2002	50	4	2	45	0.96 [0.87, 1.00]	0.92 [0.80, 0.98]
Carroccio 2002a	24	15	0	168	1.00 [0.86, 1.00]	0.92 [0.87, 0.95]
Bardella 2001	40	2	0	108	1.00 [0.91, 1.00]	0.98 [0.94, 1.00]



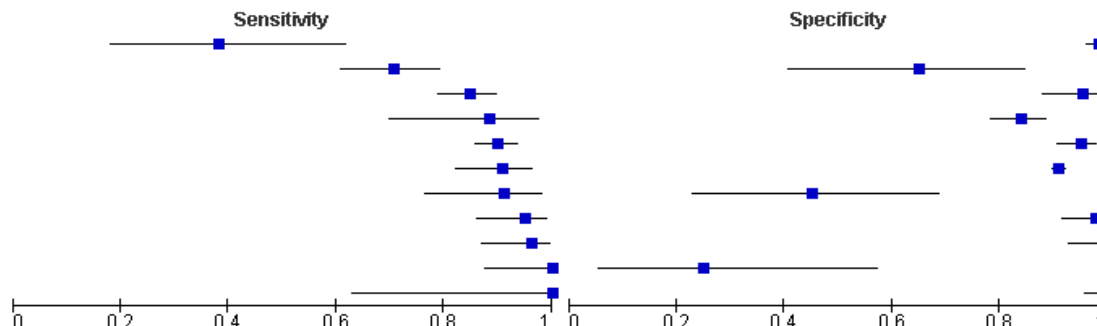
**IgG tTG GP**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Troncone 1999	11	1	37	62	0.23 [0.12, 0.37]	0.98 [0.91, 1.00]



**IgA tTG HR**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Emami 2008	8	6	13	323	0.38 [0.18, 0.62]	0.98 [0.96, 0.99]
Abrams 2006	72	7	30	13	0.71 [0.61, 0.79]	0.65 [0.41, 0.85]
Carroccio 2006	162	4	29	78	0.85 [0.79, 0.90]	0.95 [0.88, 0.99]
Reeves 2006	23	37	3	191	0.88 [0.70, 0.98]	0.84 [0.78, 0.88]
Tesei 2003	225	9	25	167	0.90 [0.86, 0.93]	0.95 [0.91, 0.98]
Hopper 2008	70	175	7	1748	0.91 [0.82, 0.96]	0.91 [0.90, 0.92]
Lui 2005	31	11	3	9	0.91 [0.76, 0.98]	0.45 [0.23, 0.68]
Niveloni 2007	57	2	3	79	0.95 [0.86, 0.99]	0.98 [0.91, 1.00]
Wolters 2002	50	0	2	49	0.96 [0.87, 1.00]	1.00 [0.93, 1.00]
Lui 2003	28	9	0	3	1.00 [0.88, 1.00]	0.25 [0.05, 0.57]
Kaukinen 2000	8	0	0	84	1.00 [0.63, 1.00]	1.00 [0.96, 1.00]



**IgG tTG HR**

Study	TP	FP	FN	TN	Sensitivity	Specificity
Reeves 2006	22	25	4	203	0.85 [0.65, 0.96]	0.89 [0.84, 0.93]

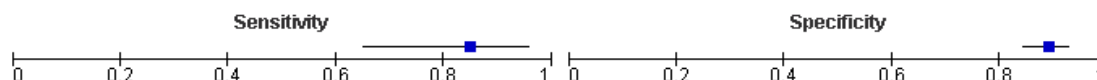


Figure 4: IgA/IgG anti-tissue transglutaminase antibodies (GP, guinea pig; HR, human recombinant)

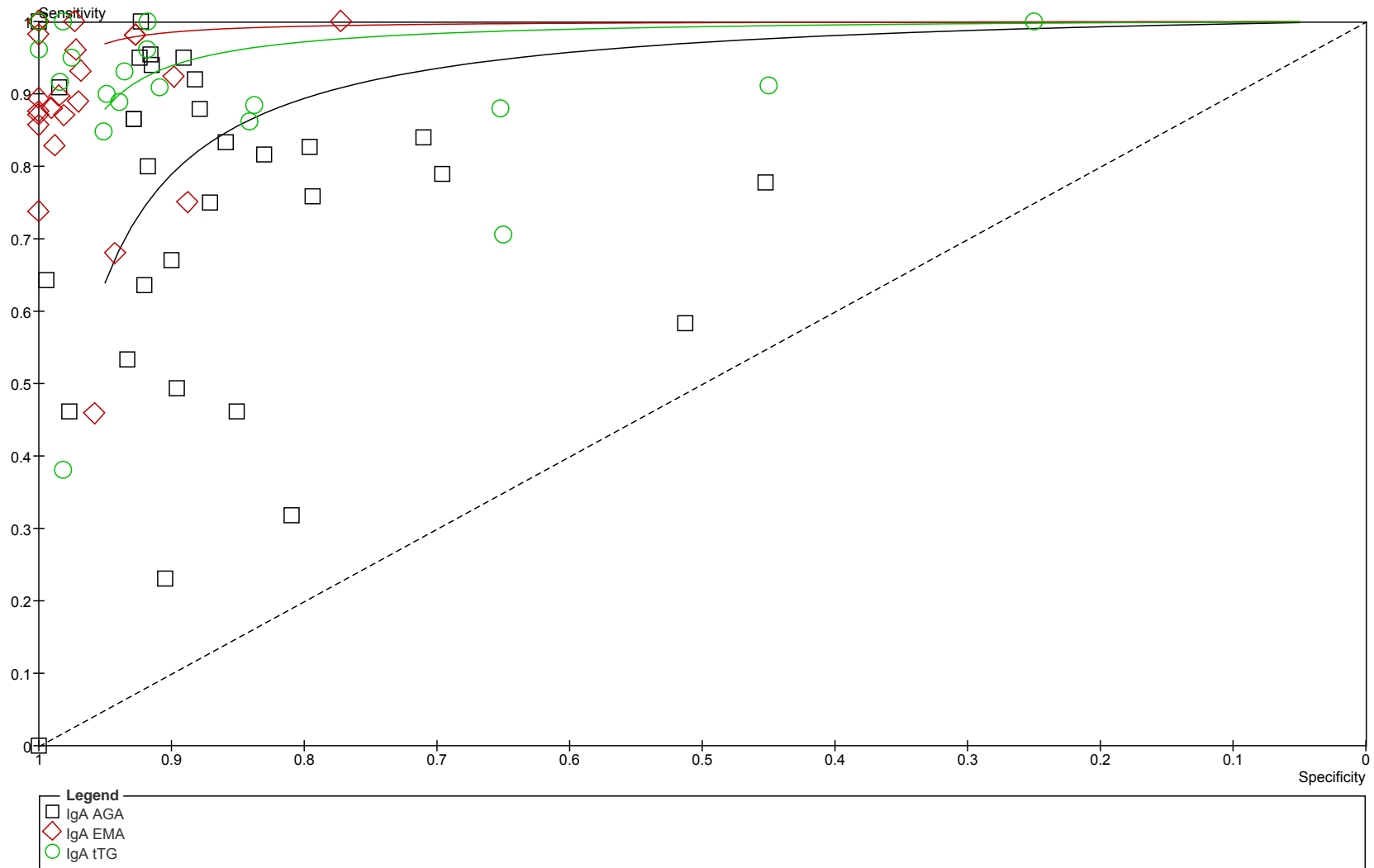


Figure 5: IgA overall results anti gliadin antibodies /anti endomysial antibodies/anti-tissue transglutaminase antibodies

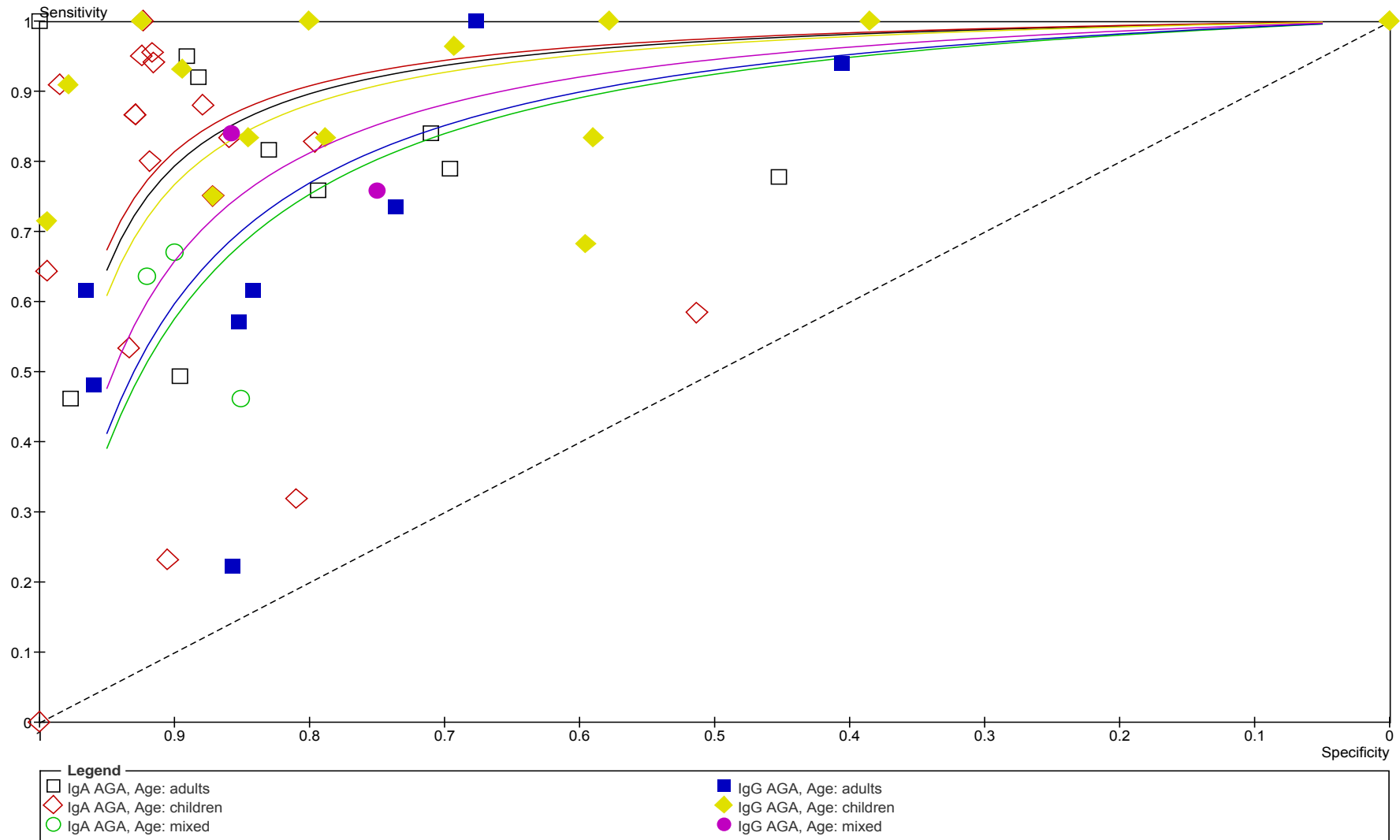


Figure 6: IgA/IgG anti gliadin antibodies adults/children/mixed

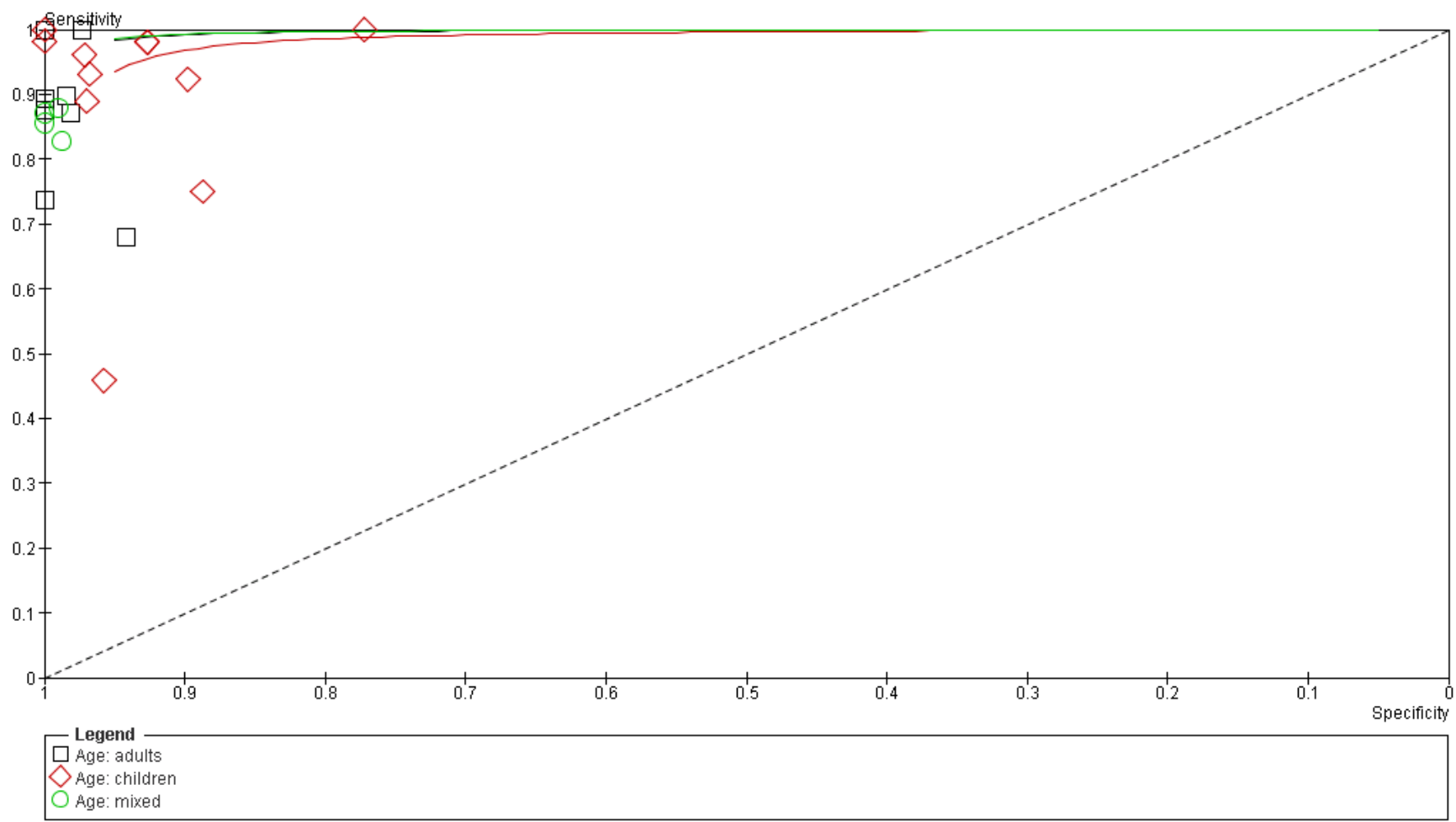


Figure 7: IgA anti endomysial antibodies adults/children/mixed

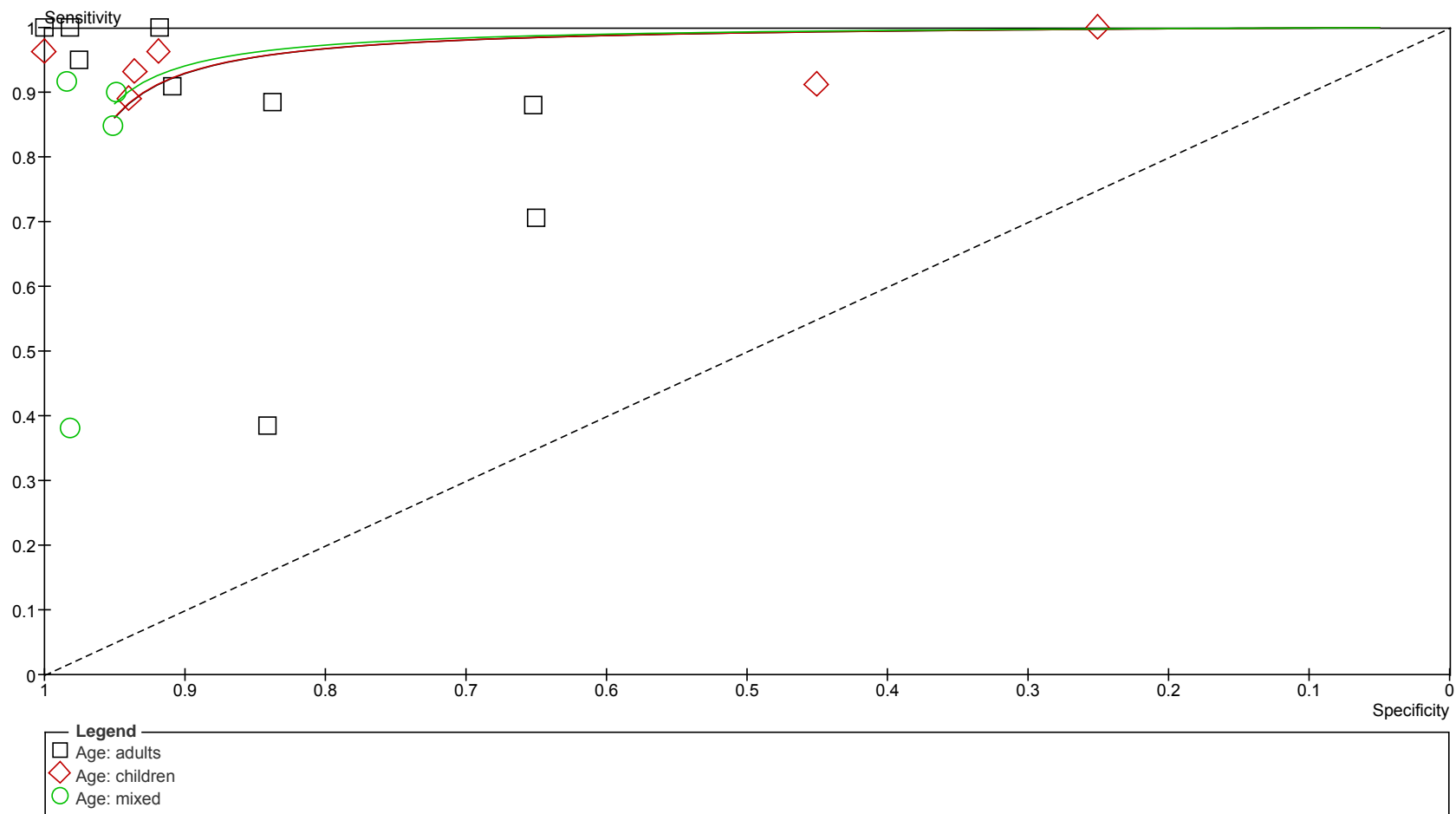


Figure 8: IgA anti-tissue transglutaminase antibodies adults/children/mixed

## Appendix 6.4 Search Strategies

### Scoping searches

Scoping searches were undertaken in May 2008 using the following websites and databases (listed in alphabetical order); browsing or simple search strategies were employed. The search results were used to provide information for scope development and project planning.

<b>Guidance/guidelines</b>	<b>Systematic reviews/economic evaluations</b>
<ul style="list-style-type: none"> <li>• British Dietetic Association</li> <li>• British Nutrition Foundation</li> <li>• British Society of Paediatric Gastroenterology, Hepatology and Nutrition</li> <li>• Canadian Medical Association Infobase</li> <li>• Coeliac UK</li> <li>• Clinical Knowledge Summaries</li> <li>• Department of Health</li> <li>• Guidelines International Network (GIN)</li> <li>• National Guideline Clearing House (US)</li> <li>• National Health and Medical Research Council (Australia)</li> <li>• National Institute for Health and Clinical Excellence (NICE) - guidance published &amp; in development</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical Evidence</li> <li>• Cochrane Database of Systematic Reviews (CDSR)</li> <li>• Database of Abstracts of Reviews of Effects (DARE)</li> <li>• Health Economic Evaluations Database (HEED)</li> <li>• Health Technology Assessment (HTA) Database</li> <li>• NHS Economic Evaluation Database (NHS EED)</li> <li>• NHS R&amp;D Service Delivery and Organisation (NHS SDO) Programme</li> <li>• National Institute for Health Research (NIHR) Health Technology Assessment Programme</li> <li>• TRIP Database</li> </ul>

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<ul style="list-style-type: none"><li>• National Institute for Health and Clinical Excellence (NICE) - topic selection</li><li>• National Library for Health (NLH) – National Library of Guidelines</li><li>• National Library for Health (NLH) Protocols and Care Pathways Database</li><li>• National Library for Health (NLH) Specialist Libraries</li><li>• New Zealand Guidelines Group</li><li>• Royal College of General Practitioners</li><li>• Royal College of Nursing</li><li>• Royal College of Paediatrics and Child Health</li><li>• Royal College of Physicians</li><li>• Royal Society of Medicine</li><li>• Scottish Intercollegiate Guidelines Network (SIGN)</li></ul>	
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### **Main searches**

#### **Prevalence of coeliac disease**

The following sources were searched to answer questions relating to the prevalence of coeliac disease (see also section 2.1.1 in the main guideline):

- what is the prevalence rate of coeliac disease, nationally and internationally?

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- are there ethnic groups where coeliac disease is more prevalent?
- is there any difference in the occurrence between males and females?
- what is the risk of coeliac disease in first-degree relatives?

The website searches were conducted between the 17 – 24 July 2008.

### *Websites searched:*

- American Celiac Disease Alliance
- American Gastroenterology Association Institute
- BBC Health: Coeliac disease
- British Society of Gastroenterology
- Canadian Celiac Association
- Celiac Disease Foundation
- Celiac Sprue Association
- Clinical Evidence
- Coeliac
- CREST
- CureReseach
- Department of Health
- eMedicine
- Gluten Intolerance Group of North America
- The Information Centre for Health and Social Care
- Health and Personal Social Services Statistics
- Health Statistics Quarterly
- Health Statistics Wales
- Health Survey
- North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)
- National Foundation for Celiac Awareness
- National Institutes of Health
- National Statistics
- WHO Statistical Information System (WHOSIS)
- World Gastroenterology Organisation

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The database searches were undertaken on 25 July 2008.

### *Databases searched:*

- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The MEDLINE search strategy is presented below. It was translated for use in MEDLINE In-Process and EMBASE.

Ovid MEDLINE(R) 1950 to July Week 3 2008

1. (coeliac adj3 disease).ti,ab.
2. (celiac adj3 disease).ti,ab.
3. (coeliac adj3 sprue).ti,ab.
4. (celiac adj3 sprue).ti,ab.
5. ((nontropical or non tropical) adj3 sprue).ti,ab.
6. ((celiac or coeliac) adj3 syndrome).ti,ab.
7. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
8. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
9. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
10. Celiac Disease/
11. or/1-10
12. (occurrence or prevalen\$ or incidence or epidemiolog\$).ti,ab.
13. (seroprevalence or seroepidemiol\$).ti,ab.
14. Prevalence/
15. Incidence/
16. Epidemiology/
17. or/12-16
18. 11 and 17
19. limit 18 to english language
20. animals/
21. humans/
22. 20 not (20 and 21)

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23. 19 not 22
24. (first adj3 relative\$.ti,ab.
25. famil\$.ti,ab.
26. Family/
27. Mothers/
28. Fathers/
29. Parents/
30. Nuclear Family/
31. Siblings/
32. Child/
33. Spouses/
34. (mother\$ or father\$ or brother\$ or sister\$ or parent\$ or child\$ or son\$ or daughter\$ or husband\$ or wive\$ or wife\$ or spouse\$ or aunt\$ or uncle\$ or sibling\$ or offspring or cousin\$).ti,ab.
35. genetic\$.ti,ab.
36. Genetic Predisposition to Disease/
37. Risk Factors/
38. risk\$.ti,ab.
39. or/24-34
40. or/35-38
41. 11 and 39 and 40
42. limit 41 to english language
43. 42 not 22
44. 23 or 42

### **The possible long-term consequences of undiagnosed coeliac disease**

The following sources were searched to answer the questions:

- for those who may be considered at increased risk of coeliac disease, is there a benefit to testing those who do not have presenting symptoms?
  - how often should those considered to be at higher risk of coeliac disease have their coeliac disease risk assessed?
- (see also section 2.2.1 in the main guideline).

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- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley and CRD website)
- Health Technology Assessment Database – HTA (Wiley and CRD website)
- CINAHL (Dialog and EBSCO)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The searches were conducted on October 3 2008.

The MEDLINE search strategy is presented below. It was translated for use in all of the other databases.

Ovid MEDLINE(R) 1950 to Sept Week 4 2008

1. (coeliac adj3 disease).ti,ab.
2. (celiac adj3 disease).ti,ab.
3. (coeliac adj3 sprue).ti,ab.
4. (celiac adj3 sprue).ti,ab.
5. ((nontropical or non tropical) adj3 sprue).ti,ab.
6. ((celiac or coeliac) adj3 syndrome).ti,ab.
7. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
8. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
9. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
10. Celiac Disease/
11. or/1-10
12. undiagnosed.ti,ab.
13. silent.ti,ab.
14. untreated.ti,ab.
15. (delay\$ adj3 diagnos\$).tw.
16. (Unrecognised or unrecognized).tw.
17. Hidden.tw.
18. Missed.tw.

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19. Misdiagnosis.tw.
20. Undetected.tw.
21. Delayed Diagnosis/
22. exp Diagnostic Error/
23. or/12-22
24. 11 and 23
25. (severe adj3 sepsis).tw.
26. septicemia.tw.
27. (blood adj3 poisoning).tw.
28. Sepsis/
29. Ricketts.tw.
30. Ricketts/
31. ((nonhodgkin or non-hodgkin) adj3 lymphoma\$.tw.
32. Lymphoma, Non-Hodgkin/
33. or/25-32
34. 33 and 11
35. 34 or 24
36. animals/
37. humans/
38. 36 not (36 and 37)
39. 35 not 38
40. limit 39 to english language

### **Signs and symptoms of coeliac disease and co-existing conditions with coeliac disease**

The following sources were searched to answer the questions:

- what are the signs and symptoms which suggest the need to investigate the possibility of a diagnosis of coeliac disease – gastrointestinal symptoms and non-gastrointestinal symptoms?
  - which co-existing conditions are associated with an increased risk of coeliac disease?
- (see also section 2.3.1 in the main guideline).

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Coeliac Disease: NICE clinical guideline Appendices vol 1 (January 2008)

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- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley and CRD website)
- Health Technology Assessment Database – HTA (Wiley and CRD website)
- CINAHL (Dialog and EBSCO)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- Clinicaltrials.gov
- metaRegister of Controlled Trials – mRCT
- UK Clinical Research Network (UKCRN) Portfolio Database

The searches were conducted on September 17 2008.

The MEDLINE search strategy for the question on the signs and symptoms of coeliac disease is presented below. It was translated for use in all of the other databases.

Ovid MEDLINE(R) 1950 to Sept Week 1 2008

1. malaise.tw.
2. fatigue.tw.
3. exhaust\$.tw.
4. Fatigue/
5. or/1-4
6. (weight adj3 loss).tw.
7. (weight adj3 reduction).tw.
8. malnutrition.tw.
9. Weight Loss/
10. or/6-9
11. (abdominal adj3 (distension or pain or bloat\$ or cramp\$)).tw.
12. (stomach adj3 (distension or pain or bloat\$ or cramp\$)).tw.
13. Abdominal Pain/
14. or/11-13
15. (nausea or vomit\$).tw.

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16. emesis.tw.
17. Vomiting/
18. Nausea/
19. or/15-18
20. diarrhoea.tw.
21. Diarrhea/
22. constipat\$.tw.
23. (colonic adj3 inertia).tw.
24. Constipation/
25. steatorrhoea.tw.
26. Steatorrhea/
27. (aphthous adj3 ulcer\$.tw.
28. (canker adj3 sore\$.tw.
29. (oral adj3 ulcer\$.tw.
30. (aphthous adj3 stomatitis).tw.
31. (mouth adj3 ulcer\$.tw.
32. Oral Ulcer/
33. Stomatitis, Aphthous/
34. (iron adj3 deficien\$.tw.
35. (vitamin adj3 (k or d) adj3 deficien\$.tw.
36. Anemia, Iron-Deficiency/
37. peripheral neuropath\$.tw.
38. (peripheral adj3 nerve adj3 disease).tw.
39. Peripheral Nervous System Diseases/
40. (Peripheral adj3 oedema).tw.
41. infertility.tw.
42. (reduced adj3 fertility).tw.
43. (recurrent adj3 miscarriage).tw.
44. Infertility/
45. cerebrospinal degeneration\$.tw.
46. (short adj stature).tw.
47. (growth adj3 disorder).tw.
48. Growth Disorders/

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49. osteoporosis.tw.
50. osteopenia.tw.
51. Osteoporosis/
52. flatulence.tw.
53. flatus.tw.
54. Flatulence/
55. (irritable adj3 bowel adj3 syndrome).tw.
56. ibs.tw.
57. Irritable Bowel Syndrome/
58. (delayed adj3 puberty).tw.
59. Puberty, Delayed/
60. headache\$.tw.
61. Headache/
62. (unexplained adj3 ataxia).tw.
63. epilepsy.tw.
64. Epilepsy/
65. (depression or anxiety).tw.
66. Depression/
67. Anxiety/
68. (enamel adj3 defect\$.tw.
69. (tooth adj3 discoloration).tw.
70. (tooth adj3 discolouration).tw.
71. arthritis.tw.
72. Arthritis/
73. or/15-72
74. 73 or 19 or 10 or 14 or 5
75. "Signs and Symptoms"/
76. ((sign or signs) adj5 symptom\$.tw.
77. Risk Factors/
78. factor\$.tw.
79. predict\$.tw.
80. or/75-79
81. 74 or 80

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82. (coeliac adj3 disease).ti,ab.
83. (celiac adj3 disease).ti,ab.
84. (coeliac adj3 sprue).ti,ab.
85. (celiac adj3 sprue).ti,ab.
86. ((nontropical or non tropical) adj3 sprue).ti,ab.
87. ((celiac or coeliac) adj3 syndrome).ti,ab.
88. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
89. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
90. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
91. Celiac Disease/
92. or/82-91
93. 92 and 81
94. Animals/
95. Humans/
96. 94 not (94 and 95)
97. 93 not 96
98. limit 97 to english language

The MEDLINE search strategy for the question on co-existing conditions is presented below. It was translated for use in all of the other databases.

Ovid MEDLINE(R) 1950 to Sept Week 1 2008

1. (coeliac adj3 disease).ti,ab.
2. (celiac adj3 disease).ti,ab.
3. (coeliac adj3 sprue).ti,ab.
4. (celiac adj3 sprue).ti,ab.
5. ((nontropical or non tropical) adj3 sprue).ti,ab.
6. ((celiac or coeliac) adj3 syndrome).ti,ab.
7. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
8. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
9. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.

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10. Celiac Disease/
11. (diabet\$ or (wolfram adj3 syndrome) or (impaired adj3 glucose adj3 intolerance)).ti,ab.
12. Diabetes Mellitus, Type 1/
13. (thyroiditis or (hashimoto adj3 disease)).ti,ab.
14. exp Thyroiditis/
15. (addison\$ adj3 disease).ti,ab.
16. (adrenal adj3 insufficiency).ti,ab.
17. hypocortisolism.ti,ab.
18. hypocorticism.ti,ab.
19. hypoadrenalism\$.ti,ab.
20. Addison Disease/
21. lupus.tw.
22. exp Lupus Erythematosus, Systemic/
23. (auto adj3 immune adj3 (liver or hepatitis)).tw.
24. Hepatitis, Autoimmune/
25. (turner\$ adj3 syndrome).ti,ab.
26. (bonnevie-ullrich adj3 syndrome).ti,ab.
27. (gonadal adj3 dysgenesis).ti,ab.
28. Turner Syndrome/
29. (alopecia or (follicular adj3 mucinosis)).ti,ab.
30. baldness.ti,ab.
31. exp Alopecia/
32. iga deficienc\$.ti,ab.
33. IgA Deficiency/
34. (down\$ adj3 syndrome).ti,ab.
35. (trisomy adj3 (hypocorticism or "21")).ti,ab.
36. Down Syndrome/
37. (william\$ adj3 syndrome).ti,ab.
38. (elfin adj3 facies adj3 syndrome).ti,ab.
39. Williams Syndrome/
40. ((Sjogren\$ or sjoegren\$) adj3 Syndrome).ti,ab.
41. Sjogren's Syndrome/
42. Comorbidity/

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43. (co-morbid\$ or comorbid\$ or co-exist\$ or coexist\$ or co-occur\$ or cooccur\$).ti,ab.
44. or/1-10
45. or/11-43
46. 44 and 45
47. Animals/
48. Humans/
49. 47 not (47 and 48)
50. 46 not 49
51. limit 50 to english language

### **The use of serological tests in the diagnostic process for coeliac disease**

The following sources were searched to answer the questions:

- what information do patients need firstly to decide whether to undergo serological testing, and if being tested do patients need to ensure that test results are as accurate as possible?
  - what is the sensitivity and specificity of serological tests for coeliac disease? are these sensitivity/specificity results different in any specified subgroups?
  - which serological test is the appropriate first option for coeliac disease?
  - depending on test results, should more than one test be used and if so what is the sequence of testing for coeliac disease?  
(see also section 2.4.1 in the main guideline).
- 
- Cochrane Database of Systematic Reviews – CDSR (Wiley)
  - Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
  - Database of Abstracts of Reviews of Effects – DARE (Wiley and CRD website)
  - Health Technology Assessment Database – HTA (Wiley and CRD website)
  - CINAHL (Dialog and EBSCO)
  - EMBASE (Ovid)
  - MEDLINE (Ovid)
  - MEDLINE In-Process (Ovid)
  - Clinicaltrials.gov
  - metaRegister of Controlled Trials – mRCT
  - UK Clinical Research Network (UKCRN) Portfolio Database

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The searches were conducted on August 14 2008.

The MEDLINE search strategy presented below was used to identify information to answer all four questions. It was translated for use in all of the other databases.

Ovid MEDLINE(R) 1950 to Aug Week 1 2008

1. (coeliac adj3 disease).ti,ab.
2. (celiac adj3 disease).ti,ab.
3. (coeliac adj3 sprue).ti,ab.
4. (celiac adj3 sprue).ti,ab.
5. ((nontropical or non tropical) adj3 sprue).ti,ab.
6. ((celiac or coeliac) adj3 syndrome).ti,ab.
7. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
8. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
9. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
10. Celiac Disease/
11. or/1-10
12. (endomysi\$ adj3 antibod\$).ti,ab.
13. (immunoglobulin adj3 endomysi\$).ti,ab.
14. ((anti-endomysi\$ or antiendomysi\$ or anti endomysi\$) adj3 antibod\$).ti,ab.
15. ((iga or igg) adj3 endomysi\$).ti,ab.
16. ((iga or igg) adj3 (anti-endomysi\$ or antiendomysi\$ or anti endomysi\$)).ti,ab.
17. (immunoglobulin adj3 (anti-endomysi\$ or antiendomysi\$ or anti endomysi\$)).ti,ab.
18. (iga-ema or igg-ema).ti,ab.
19. ema.ti,ab.
20. or/12-19
21. 11 and 20
22. (transglutaminase adj3 antibod\$).ti,ab.
23. (tissue adj3 transglutaminase adj3 antibod\$).ti,ab.
24. (((anti-tissue or antitissue or anti tissue) adj3 transglutaminase) and antibod\$).ti,ab.
25. (immunoglobulin adj3 transglutaminase).ti,ab.

DRAFT FOR CONSULTATION

26. ((iga or igg) adj3 transglutaminase).ti,ab.
27. (anti-httg or anti-htg).ti,ab.
28. ((anti-human or antihuman or anti human) adj3 transglutaminase adj3 antibod\$).ti,ab.
29. transglutaminases/
30. tTG.ti,ab.
31. or/22-30
32. 11 and 31
33. (gliadin adj3 antibod\$).ti,ab.
34. (immunoglobulin adj3 gliadin).ti,ab.
35. ((antigliadin or anti-gliadin or anti gliadin) adj3 antibod\$).ti,ab.
36. ((igg or iga) adj3 gliadin).ti,ab.
37. ((igg or iga) adj3 (antigliadin or anti-gliadin or anti gliadin)).ti,ab.
38. (immunoglobulin adj3 (antigliadin or anti-gliadin or anti gliadin)).ti,ab.
39. (elisa adj3 test\$).ti,ab.
40. Gliadin/ and Immunoglobulins/
41. AGA.ti,ab.
42. or/33-41
43. 11 and 42
44. (human adj3 (leukocyte\$ or leucocyte\$) adj3 antigen\$).ti,ab.
45. (hla adj3 typ\$).ti,ab.
46. (dr3 adj3 dq2).ti,ab.
47. (dr4 adj3 dq8).ti,ab.
48. (hla adj3 dq2).ti,ab.
49. (hla adj3 dq8).ti,ab.
50. HLA-DQ Antigens/
51. HLA-DR3 Antigen/
52. or/44-51
53. 11 and 52
54. Serologic Tests/
55. (serologic adj3 test\$).ti,ab.
56. 54 or 55
57. 11 and 56
58. 21 or 32 or 43 or 53 or 57

## DRAFT FOR CONSULTATION

59. limit 58 to english language
60. animals/
61. humans/
62. 60 not (60 and 61)
63. 59 not 62

### Health economics

The following sources were searched to identify economic evaluations and quality of life data relating to serological tests for coeliac disease (see also section 2.4.6 in the main guideline):

- Health Economic Evaluations Database – HEED (Wiley)
- NHS Economic Evaluation Database – NHS EED (Wiley and CRD website)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The searches were undertaken on August 14th 2008.

The MEDLINE search strategy is presented below. It was translated for use in other databases.

Ovid MEDLINE(R) 1950 to Aug Week 1 2008

1. (coeliac adj3 disease).ti,ab.
2. (celiac adj3 disease).ti,ab.
3. (coeliac adj3 sprue).ti,ab.
4. (celiac adj3 sprue).ti,ab.
5. ((nontropical or non tropical) adj3 sprue).ti,ab.
6. ((celiac or coeliac) adj3 syndrome).ti,ab.
7. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
8. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
9. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.

## DRAFT FOR CONSULTATION

10. Celiac Disease/

11. or/1-10

12. (endomysi\$ adj3 antibod\$).ti,ab.

13. (immunoglobulin adj3 endomysi\$).ti,ab.

14. ((anti-endomysi\$ or antiendomysi\$ or anti endomysi\$) adj3 antibod\$).ti,ab.

15. ((iga or igg) adj3 endomysi\$).ti,ab.

16. ((iga or igg) adj3 (anti-endomysi\$ or antiendomysi\$ or anti endomysi\$)).ti,ab.

17. (immunoglobulin adj3 (anti-endomysi\$ or antiendomysi\$ or anti endomysi\$)).ti,ab.

18. (iga-ema or igg-ema).ti,ab.

19. ema.ti,ab.

20. or/12-19

21. 11 and 20

22. (transglutaminase adj3 antibod\$).ti,ab.

23. (tissue adj3 transglutaminase adj3 antibod\$).ti,ab.

24. (((anti-tissue or antitissue or anti tissue) adj3 transglutaminase) and antibod\$).ti,ab.

25. (immunoglobulin adj3 transglutaminase).ti,ab.

26. ((iga or igg) adj3 transglutaminase).ti,ab.

27. (anti-httg or anti-htg).ti,ab.

28. ((anti-human or antihuman or anti human) adj3 transglutaminase adj3 antibod\$).ti,ab.

29. transglutaminases/

30. tTG.ti,ab.

31. or/22-30

32. 11 and 31

33. (gliadin adj3 antibod\$).ti,ab.

34. (immunoglobulin adj3 gliadin).ti,ab.

35. ((antigliadin or anti-gliadin or anti gliadin) adj3 antibod\$).ti,ab.

36. ((igg or iga) adj3 gliadin).ti,ab.

37. ((igg or iga) adj3 (antigliadin or anti-gliadin or anti gliadin)).ti,ab.

38. (immunoglobulin adj3 (antigliadin or anti-gliadin or anti gliadin)).ti,ab.

39. (elisa adj3 test\$).ti,ab.

40. Gliadin/ and Immunoglobulins/

41. AGA.ti,ab.

42. or/33-41

Coeliac Disease: NICE clinical guideline Appendices vol 1 (January 2008)

Page 43 of 74

DRAFT FOR CONSULTATION

43. 11 and 42
  44. (human adj3 (leukocyte\$ or leucocyte\$) adj3 antigen\$).ti,ab.
  45. (hla adj3 typ\$).ti,ab.
  46. (dr3 adj3 dq2).ti,ab.
  47. (dr4 adj3 dq8).ti,ab.
  48. (hla adj3 dq2).ti,ab.
  49. (hla adj3 dq8).ti,ab.
  50. HLA-DQ Antigens/
  51. HLA-DR3 Antigen/
  52. or/44-51
  53. 11 and 52
  54. Serologic Tests/
  55. (serologic adj3 test\$).ti,ab.
  56. 54 or 55
  57. 11 and 56
  58. 21 or 32 or 43 or 53 or 57
  59. limit 58 to english language
  60. animals/
  61. humans/
  62. 60 not (60 and 61)
  63. 59 not 62
  64. Economics/
  65. exp "Costs and Cost Analysis"/
  66. Economics, Dental/
  67. exp Economics, Hospital/
  68. exp Economics, Medical/
  69. Economics, Nursing/
  70. Economics, Pharmaceutical/
  71. Budgets/
  72. exp Models, Economic/
  73. Markov Chains/
  74. Monte Carlo Method/
  75. Decision Trees/
- Coeliac Disease: NICE clinical guideline Appendices vol 1 (January 2008)

## DRAFT FOR CONSULTATION

76. econom\$.tw.
77. cba.tw.
78. cea.tw.
79. cua.tw.
80. markov\$.tw.
81. (monte adj carlo).tw.
82. (decision adj2 (tree\$ or analys\$)).tw.
83. (cost or costs or costing\$ or costly or costed).tw.
84. (price\$ or pricing\$).tw.
85. budget\$.tw.
86. expenditure\$.tw.
87. (value adj2 (money or monetary)).tw.
88. (pharmacoeconomic\$ or (pharmaco adj economic\$)).tw.
89. or/64-88
90. "Quality of Life"/
91. quality of life.tw.
92. "Value of Life"/
93. Quality-Adjusted Life Years/
94. quality adjusted life.tw.
95. (qaly\$ or qald\$ or qale\$ or qtime\$).tw.
96. disability adjusted life.tw.
97. daly\$.tw.
98. Health Status Indicators/
99. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
100. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
101. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
102. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
103. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
104. (euroqol or euro qol or eq5d or eq 5d).tw.
105. (qol or hql or hqol or hrqol).tw.
106. (hye or hyes).tw.
107. health\$ year\$ equivalent\$.tw.

## DRAFT FOR CONSULTATION

108. utilit\$.tw.
109. (hui or hui1 or hui2 or hui3).tw.
110. disutili\$.tw.
111. rosser.tw.
112. quality of wellbeing.tw.
113. quality of well-being.tw.
114. qwb.tw.
115. willingness to pay.tw.
116. standard gamble\$.tw.
117. time trade off.tw.
118. time tradeoff.tw.
119. tto.tw.
120. or/90-119
121. 89 or 120
122. 63 and 121

### **Additional searches for the de novo economic model**

Additional searches were undertaken to identify inputs for the de novo economic model using the following sources (see also section 2.4.6 in the main guideline).

- NHS Economic Evaluation Database – NHS EED (Wiley and CRD website)
- Health Economic Evaluations Database – HEED (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley and CRD website)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The searches were undertaken on October 23rd 2008 to identify data for the economic model on mortality and health outcomes for coeliac disease and to update the strategy presented in (Dretzke et al 2004) on adherence to gluten free diet:

The MEDLINE search strategy to identify health outcomes data is presented below. It was translated for use in other databases.

DRAFT FOR CONSULTATION

Ovid MEDLINE(R) 1950 to October Week 3 2008

1. (coeliac adj3 disease).ti,ab.
2. (celiac adj3 disease).ti,ab.
3. (coeliac adj3 sprue).ti,ab.
4. (celiac adj3 sprue).ti,ab.
5. ((nontropical or non tropical) adj3 sprue).ti,ab.
6. ((celiac or coeliac) adj3 syndrome).ti,ab.
7. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
8. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
9. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
10. Celiac Disease/
11. or/1-10
12. "Quality of Life"/
13. quality of life.tw.
14. "Value of Life"/
15. Quality-Adjusted Life Years/
16. quality adjusted life.tw.
17. (qaly\$ or qald\$ or qale\$ or qtime\$).tw.
18. disability adjusted life.tw.
19. daly\$.tw.
20. Health Status Indicators/
21. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
22. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
23. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
24. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
25. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
26. (euroqol or euro qol or eq5d or eq 5d).tw.
27. (qol or hql or hqol or hrqol).tw.
28. (hye or hyes).tw.
29. health\$ year\$ equivalent\$.tw.
30. utilit\$.tw.

## DRAFT FOR CONSULTATION

31. (hui or hui1 or hui2 or hui3).tw.
32. disutili\$.tw.
33. rosser.tw.
34. quality of wellbeing.tw.
35. quality of well-being.tw.
36. qwb.tw.
37. willingness to pay.tw.
38. standard gamble\$.tw.
39. time trade off.tw.
40. time tradeoff.tw.
41. tto.tw.
42. or/12-41
43. 42 and 11
21. limit 43 to yr="2002 - 2008"

The MEDLINE search strategy to identify systematic reviews of mortality is presented below. It was translated for use in other databases.

Ovid MEDLINE(R) 1950 to October Week 3 2008

1. (coeliac adj3 disease).ti,ab.
2. (celiac adj3 disease).ti,ab.
3. (coeliac adj3 sprue).ti,ab.
4. (celiac adj3 sprue).ti,ab.
5. ((nontropical or non tropical) adj3 sprue).ti,ab.
6. ((celiac or coeliac) adj3 syndrome).ti,ab.
7. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
8. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
9. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
10. Celiac Disease/
11. or/1-10
12. mortality.ti,ab.
13. (Life adj3 expectancy).ti,ab.

DRAFT FOR CONSULTATION

14. (life adj3 span).ti,ab.
15. longevity.ti,ab.
16. (length adj3 life).ti,ab.
17. (death adj3 rate\$).ti,ab.
18. Mortality/
19. Life Expectancy/
20. Longevity/
21. or/12-20
22. 11 and 21
23. Meta-Analysis/
24. Meta-Analysis.pt.
25. Meta-Analysis as Topic/
26. Review/
27. Review.pt.
28. exp Review Literature as Topic/
29. (metaanaly\$ or metanaly\$ or (meta adj2 analy\$)).tw.
30. (review\$ or overview\$).ti.
31. (systematic\$ adj4 (review\$ or overview\$)).tw.
32. ((quantitative\$ or qualitative\$) adj4 (review\$ or overview\$)).tw.
33. ((studies or trial\$) adj1 (review\$ or overview\$)).tw.
34. (integrat\$ adj2 (research or review\$ or literature)).tw.
35. (pool\$ adj1 (analy\$ or data)).tw.
36. (handsearch\$ or (hand adj2 search\$)).tw.
37. (manual\$ adj2 search\$).tw.
38. or/23-37
39. animals/
40. humans/
41. 39 not (39 and 40)
42. 38 not 41
43. 42 and 22
21. limit 43 to yr="2002 - 2008"

## DRAFT FOR CONSULTATION

The MEDLINE search strategy to identify studies on adherence to gluten free diet is presented below. It was translated for use in other databases.

Ovid MEDLINE(R) 1950 to October Week 3 2008

1. (coeliac adj3 disease).ti,ab.
2. (celiac adj3 disease).ti,ab.
3. (coeliac adj3 sprue).ti,ab.
4. (celiac adj3 sprue).ti,ab.
5. ((nontropical or non tropical) adj3 sprue).ti,ab.
6. ((celiac or coeliac) adj3 syndrome).ti,ab.
7. (gluten adj3 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
8. ((glutenin or gliadin) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
9. ((wheat or barley or rye or oat\$) adj3 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).ti,ab.
10. Celiac Disease/
11. or/1-10
12. complian\$.ti,ab.
13. adhere\$.ti,ab.
14. concordance.ti,ab.
15. refus\$.ti,ab.
16. agreement.ti,ab.
17. Patient Compliance/
18. cooperation.ti,ab.
19. or/12-18
20. 11 and 19
21. limit 20 to yr="2002 - 2008"

## ***Appendix 6.5 Health Economics Evidence Report & Evidence Tables***

### **Health economic evidence report**

#### ***Aims***

An economic evaluation was undertaken to estimate the cost effectiveness of serological tests for coeliac disease in patients who present with signs and symptoms of the disease.

#### ***Method***

There are no published economic evaluations that examine the cost effectiveness of serological tests to diagnose coeliac disease in patients presenting with signs and symptoms for a UK population using QALYs as an outcome measure. This suggests that the development of a new economic model is required.

Serological tests examined in the new model were IgA tTGA and IgA EMA tests. These were analysed alone and in combination followed by biopsy for positive results. Strategies with separate IgA deficiency testing were also included. A 'no test' strategy and a biopsy only strategy were included. These final two strategies would not generally be considered in clinical practice but are included for comparison with the other strategies. AGA tests and IgG tests as first line tests were not examined in the model in line with the results of the clinical systematic review of their diagnostic accuracy. The GDG also considered their use to be uncommon in current clinical practice.

**Table A1 Outline of strategies included**

<b>Strategy number</b>	<b>Description</b>
1	IgA tTGA test followed by biopsy in the case of a positive result
2	IgA EMA test followed by biopsy in the case of a positive result
3	IgA tTGA then IgA EMA in a two step strategy followed by a biopsy if IgA tTGA was positive then IgA EMA was positive
4	IgA tTGA and IgA EMA in test combination followed by a biopsy if both tests were positive
5	IgA tTGA and IgA EMA in test combination followed by a biopsy if either test was positive
6	IgA tTGA test followed by IgA deficiency test and biopsy in the case of a positive result
7	IgA EMA test followed by IgA deficiency test and biopsy in the case of a positive result
8	Biopsy all patients
9	No test for all patients

The strategies were based on a UK based, good quality study, by Hopper et al (2008) and on agreement with the GDG. Data on sensitivity and specificity were also taken from this study. Hopper et al (2008) evaluated the sensitivity and specificity of several serological test strategies in 2000 patients who had been referred for biopsy. The results were confirmed by biopsy. As the study was conducted within a UK setting, it provides direct evidence on which to base the economic model.

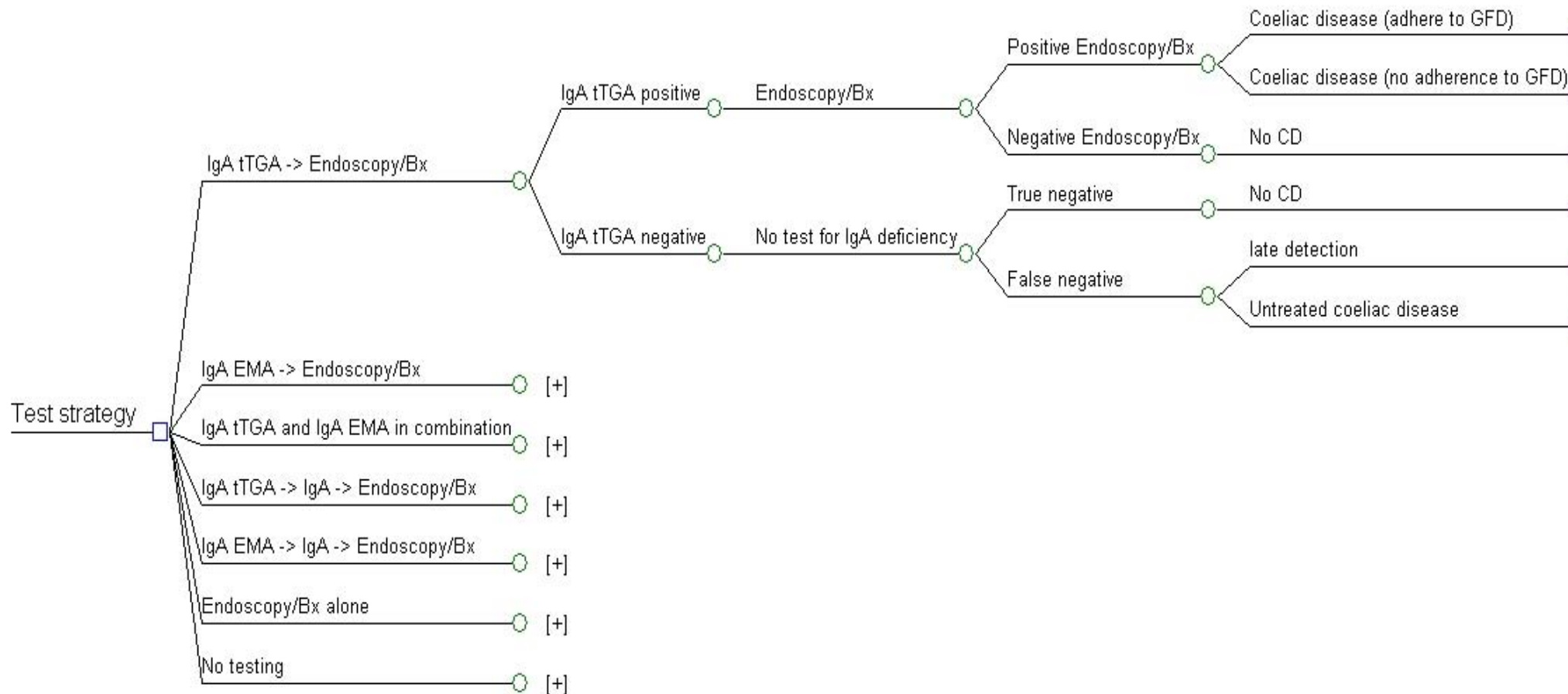
The model provides an estimate of costs and health outcomes in terms of quality-adjusted life years (QALYs). The model was built and analysed using TreeAge Pro 2007 Suite (TreeAge software, Inc) and adopted a lifetime horizon. Several test strategies were examined and compared with a 'no testing' strategy. The structure of the decision tree was agreed with the GDG and was informed by previous cost effectiveness studies as outlined in section 2.4.4 of the main guideline. Patients accrued costs and utilities depending on their pathway through the model. At the end of the decision tree patients then

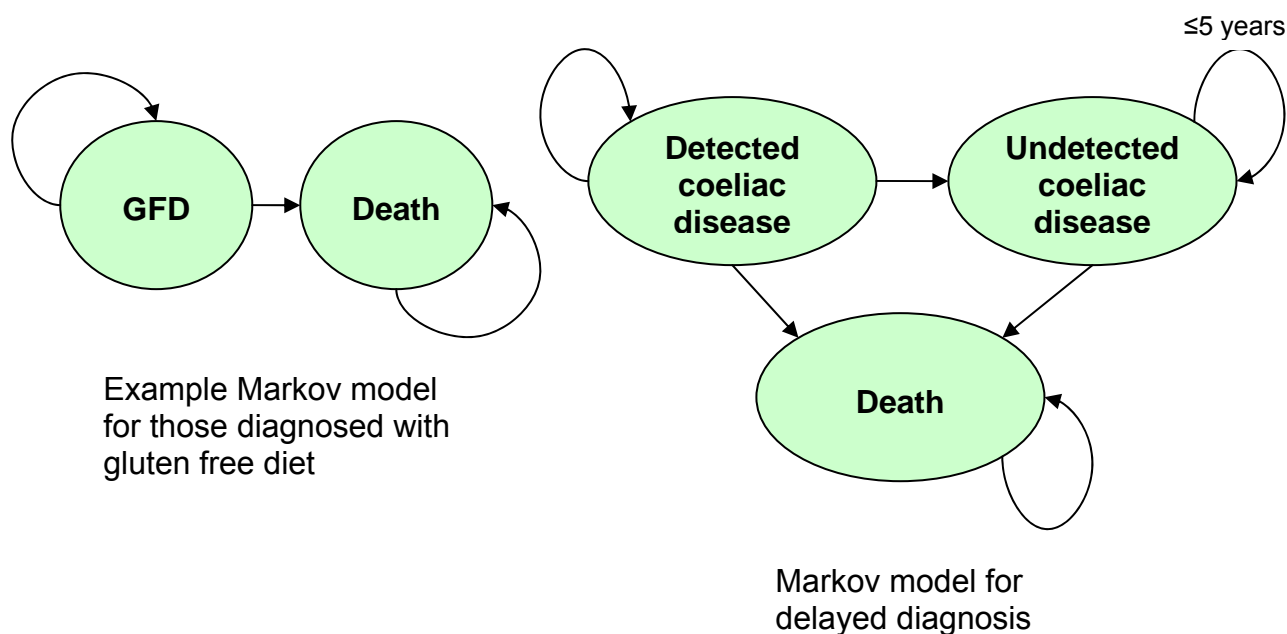
entered a Markov model with states reflecting their eventual diagnosis, that is, diagnosed as having coeliac disease, no diagnosis of coeliac disease or undiagnosed coeliac disease. Patients accrued costs and utilities linked with these states until death. A diagrammatic representation of one of the strategies in the decision tree is given in figure A1. A diagrammatic representation of the Markov model for patients who are on a gluten free diet and who are adhering to that diet and of the Markov model for people whose coeliac disease is delayed is outlined in figure A2 below.

Simple one-way deterministic sensitivity analyses were used to explore the contribution of individual parameters to overall uncertainty in the cost-effectiveness estimates.

Note: Probabilistic sensitivity analysis will be considered and any results will be available for the final version of the guideline.

Figure A1 Diagrammatic representation of strategy 1 in the decision tree





**Figure A2 Markov model for patients on a gluten free diet**

### ***Probabilities and diagnostic accuracy data***

Table A2 sets out the probabilities and other individual parameter estimates used in the model.

### **Diagnostic accuracy of serological tests**

Sensitivity and specificity values for each of the strategies were taken from the clinical systematic review. There were a large number of papers included in the systematic review. These data were not formally synthesized due to reasons discussed in section 2.4.4. In order to have appropriate data for the economic model, these papers were carefully reviewed. Hopper et al (2008) represents a UK patient population suspected of having coeliac disease and therefore the data contained in this paper was thought to be suitable for use in the economic analysis by the GDG. Sensitivity and specificity values were tested in sensitivity analysis using confidence intervals provided in Hopper et al (2008) as an estimate of the uncertainty surrounding these data. The biopsy and endoscopy were assumed to provide the gold standard test in the model and therefore their sensitivity and specificity is assumed to be 100%. In strategies where a separate

IgA deficiency test is performed it is also assumed that this test had 100% sensitivity and specificity on the advice of the GDG.

### **Prevalence of coeliac disease in a population with signs and symptoms**

The clinical systematic review estimated the prevalence of coeliac disease within UK based national studies to be between 0.8% and 1.9%. This is a broadly similar rate to other international studies. The prevalence of coeliac disease in a population of patients who present with signs and symptoms is likely to be higher than in the general population. Hopper et al (2008) represents a patient population with suspected coeliac disease, therefore the data contained in this study on the prevalence of coeliac disease were considered suitable for use in the economic analysis by the GDG. The prevalence used in our analysis was supported by other studies that examined a patient population with an elevated prevalence of coeliac disease (Mein and Ladabaum et al 2004, Swigonski et al 2008 and the NICE guideline on irritable bowel syndrome in adults (NICE clinical guideline 61 (2008). Available from [www.nice.org.uk/CG061](http://www.nice.org.uk/CG061))).

### **Life expectancy**

An additional literature search was carried out in order to identify systematic reviews on the life expectancy of people with coeliac disease. No full systematic reviews were identified. The base case assumptions were made following a review of the available literature on mortality from the clinical and economic literature searches. Life expectancy for those with diagnosed coeliac disease and adhering to a gluten free diet is assumed to be the same as for the general population in the base case (Holmes et al 1989). Therefore standard UK life expectancy tables have been used to estimate mortality in the model in those with no coeliac disease and in those with coeliac disease following a gluten free diet. There is evidence of an increase in malignancy and mortality for those with undiagnosed coeliac disease. This will be taken into account as reduced life expectancy in the model. We also assumed that people with diagnosed coeliac disease who do not adhere to a gluten free diet will have a reduced life expectancy. In order to do this a standard mortality ratio of 2 was applied to the standard mortality tables (Corrao et al. 2001). This results in an overall decrease in life expectancy of 7 years for undiagnosed coeliac disease. This assumption will be tested in sensitivity analysis.

**Ratio of men to women in the model**

There is evidence that coeliac disease occurs more often in women than in men. The model takes account of the difference in life expectancy according to this split. Evidence suggests an approximate 1:2 male to female ratio, (Garampazzi et al and Corrao et al 2001) and this was applied in the model.

**IgA deficiency**

Several studies have suggested that there is a higher level of IgA deficiency in those with coeliac disease than in the general population. Patients presenting with signs and symptoms suggestive of coeliac disease may therefore also be more likely to have an IgA deficiency. The model assumes a level of 0.75% which lies between the general population and coeliac disease population in the base case. This was taken from a study that examined the IgA deficiency in a population of people who were also being tested for IgA EMA (McGowan, Lyon and Butzner 2008). This is also supported by Hopper et al (2008) in which the prevalence of IgA deficiency was found to be 0.7%.

**Adherence to gluten free diet**

Not all people who are diagnosed with coeliac disease will adhere to a gluten free diet. Following a review of the literature, Dretzke et al (2004) assumed that 60% of patients adhere to a prescribed gluten free diet in their base case. We have also used this figure in the base case analysis. We recognise that there are many factors that may affect adherence and that it may be difficult to make a general assumption on how many patients follow a gluten free diet, therefore this value was tested in sensitivity analysis. In particular, the patient population in our study may be more likely to follow a gluten free diet considering that they presented with signs and symptoms.

**Probability that coeliac disease would never be detected**

There is a probability in the model that a false negative result will not be identified and represents patients whose coeliac disease is never diagnosed. This was considered to be approximately 30% based on calculations made by Dretzke et al (2004).

**Table A2 summary of model parameters, values and sources**

<b>Parameter and explanation</b>	<b>Base case value</b>	<b>Lower</b>	<b>Upper</b>	<b>Reference</b>
<b>Prevalence and life expectancy</b>				

Prevalence of coeliac disease	0.0385	0.385	0.00385	Hopper et al
Life expectancy for those with diagnosed coeliac disease and adhering to a GFD	General population	-	-	Holmes et al 1989 and life expectancy tables (government actuarial department (GAD))
Life expectancy for those with diagnosed coeliac disease who do not adhere to a GFD and those with undiagnosed coeliac disease	SMR of 2	1	3	Corrao et al. 2001
Prevalence of IgA deficiency	0.75%	0.375%	1.125%	McGowan, Lyon and Butzner 2008
Proportion of males to females	1:2	1:1	-	Garampazzi et al, Corrao et al 2001
Probability of coeliac disease never being detected	0.30			Dretzke et al
Probability of adhering to a GFD	0.60	0.3	0.9	Dretzke et al
<b>Sensitivity and specificity of serological tests (%)</b>				
Sensitivity of IgA tTGA	90.9	82.4	94.5	Hopper et al
Specificity of IgA tTGA	90.9	89.5	92.1	Hopper et al
Sensitivity of IgA EMA	87.0	77.7	92.8	Hopper et al
Specificity of IgA EMA	98.0	97.4	98.6	Hopper et al
Sensitivity of IgA tTGA then IgA EMA (2 step)	85.7	76.2	91.8	Hopper et al
Specificity of IgA tTGA then IgA EMA (2 step)	98.6	98.0	99.0	Hopper et al
Sensitivity of IgA tTGA then IgA EMA (both positive)	85.7	76.2	91.8	Hopper et al
Specificity of IgA tTGA then IgA EMA (both positive)	98.6	98.0	99.0	Hopper et al
Sensitivity of IgA tTGA then IgA EMA (either positive)	92.2	84.0	96.4	Hopper et al
Specificity of IgA tTGA then IgA EMA (either positive)	90.3	88.9	91.6	Hopper et al
IgA sensitivity and specificity	100	-	-	Assumption
Biopsy and endoscopy	100	-	-	Assumption

### Health related quality of life weights

There is a paucity of data on the utility of having coeliac disease and of being on a gluten free diet. Although the original searches for economic papers on coeliac disease included utilities and quality of life search terms, this search was specifically for serological tests used to diagnose coeliac disease. Therefore a search to identify utility studies relating to coeliac disease in general was commissioned. Several studies were identified and suggested that there is a significant decrease in quality of life for patients

with recently diagnosed coeliac disease who have not yet begun a gluten free diet. There are many factors affecting the quality of life in coeliac disease including length of time with diagnosis and adherence to a gluten free diet.

One further study was identified that examined the factors that impact health related quality of life in adults with coeliac disease who were outpatients of the digestive services units of seven Spanish hospitals (Casellas et al 2008). Data were collected for two groups, those already following a gluten free diet and those who had not yet started a gluten free diet. As part of this study EQ-5D scores were collected. Median EQ-5D scores for these patients were reported, and these showed that the median preference score was significantly higher in patients on a gluten free diet. The authors also concluded that those on a controlled gluten free diet had scores that were very similar to those of a representative sample of the Spanish general population. The population of this study is not directly applicable to the UK population and only median rather than mean values were reported. However, taking into account these limitations, it may be useful to infer from Casellas et al's results that there may be no difference in utility between patients who are on a controlled gluten free diet and those who do not have coeliac disease. It may also be useful to note that there is a substantial increase in quality of life for patients who are on gluten free diets compared with those who are not. No further studies were identified that allowed the direct calculation of utilities.

After examining the literature, Dretzke et al (2004) assumed a utility of 0.88 for treated coeliac disease with 100% compliance on a GFD taking into account both type 1 diabetes and coeliac disease (a disutility of 0.002 on in addition to having diabetes). For untreated coeliac disease (0% compliance on a GFD) the utility used was 0.82. We applied these utilities in our model. While these values aim to account for the presence of diabetes, for the purpose of the present analysis it is the difference between untreated and treated coeliac disease that was considered key. The GDG also felt that patients in our model may have a lower utility than the general population anyway, due to having a clinical suspicion of coeliac disease. We tested these values extensively in sensitivity analysis due to the high degree of uncertainty surrounding them.

**Table A3 Utility weights used in the model**

Health state	Estimate	Range	Source/comment
No CD	0.90	0.95-1	Dretzke et al (2004) / assumption
Treated CD	0.88	0.93	Dretzke et al (2004) / Casellas et al (2008)
Untreated CD	0.82	0.72	Dretzke et al (2004) / Casellas et al (2008)
Endoscopy and biopsy	-0.002	-	Dretzke et al (2004)/assumption based on one day with a utility of zero in the year adjusted for a year in health state 'no CD'

### Costs

Costs are reported for the year 2007–8 and are reported in GBP. In order to be consistent with other programmes within NICE and in accordance with the reference case developed by Technology Appraisals, the costs and benefits were discounted at 3.5% each.

### Serological tests

Costs of serological tests are difficult to estimate as there is no national tariff available. Cost of serological tests can vary greatly depending on who orders the test and how they are carried out. Economies of scale are also realised when using diagnostic equipment and therefore price may differ depending on the volume of tests carried out by the laboratory. It may also be difficult to assess costs because not everyone pays the same price. Different prices are made available for Trusts, prices for GPs and other NHS providers, and private providers. The list price from the manufacturer could be used but may not be an accurate reflection of the price paid by the NHS.

Dretzke et al (2004) estimated the cost of serological tests to the NHS by communication with laboratories. We have also taken this approach and the costs of the tests have been estimated from data provided by two laboratories in the UK following communication with a GDG member. The costs are those charged by the laboratory to GPs in the UK and include the cost of the test, staffing costs, consumables and overheads. The costs used in this economic evaluation were deemed to adequately represent the cost to the NHS of serological testing for coeliac disease by the GDG. Nominal additional fees are often charged if two serological tests are carried out. A high

fee has been assumed in this case, that is, IgA EMA test plus a nominal fee of £0.50, and this is considered to be a conservative estimate. As two of the combination test strategies have the same sensitivity and specificity, these strategies were used to assess what happens to results when the tests are carried out and charged for separately. The IgA test was also considered to be charged for as an additional nominal fee.

### **Cost of endoscopy and biopsy**

The most recent Reference Costs available do not contain the HRGv4 code linked to the correct procedure codes for endoscopy and biopsy (G551 or G651). As a result, the most recent National Tariff (08/09) has been used. The procedure code relating to diagnostic endoscopic examination of duodenum and biopsy of lesion of duodenum, is linked with HRG codes F06 and F63 (using version 3.5). The procedure relating to diagnostic endoscopic examination of jejunum and biopsy of lesion of jejunum, was also available giving HRG codes F06, F53/54 and F61. HRG code F06 was considered to be the most relevant and it is also used for both the procedure codes outlined above. Therefore a cost of £410 was used to represent the cost to the NHS of an endoscopy and biopsy for coeliac disease. Complications of this procedure were not taken into account following consideration of the literature (Spencer et al 2003) and the GDG's view that they are assumed to be very rare.

### **Gluten free diet and follow up for patients with coeliac disease**

The cost to the NHS of a gluten free diet is limited to gluten free foods available on prescription. In order to estimate the cost to the NHS, the method used by the irritable bowel syndrome in adults guideline (NICE clinical guideline 61 (2008). Available from [www.nice.org.uk/CG061](http://www.nice.org.uk/CG061)) with updated prescription costs was used. The prescription charges for all gluten free foods in 2007 were approximately £23.65 million (NHS Health and Social Care Information Centre. Prescription Cost Analysis, 2007). This was divided by the number of people with coeliac disease based on a population of 50.4 million for England and the prevalence of diagnosed coeliac disease taken from Fowell et al (2006) of 0.26%. Using this method the annual cost per diagnosed case of coeliac disease was £180.48.

### Cost of follow up for patients diagnosed with coeliac disease

Once diagnosed with coeliac disease, patients are recommended to adhere to a gluten free diet. Follow up is also recommended in the British Society of Gastroenterologist (BSG) guidelines with visits to the GP and follow up serological and other routine tests as well as visits to a dietitian. However, exact number of consultations and tests required is not clear from the guidelines and therefore an estimation of the resource use must be made. The model estimates a cost of approximately £100 per patient per year based on one GP visit, one set of serological tests, one set of routine blood tests and one dietitian visit. The cost of the GP visit was £34 and was taken from the PSSRU (2007). The cost of the dietitian visit was £46 based on a follow up visit taken from personal communication with a GDG member this is because the PSSRU only gives the cost of a hospital based dietitian rather than a dietitian operating in primary care or specialist clinic. The costs of the tests were assumptions based on communication with the GDG and laboratories. Due to the uncertainty around costs of tests, the cost of follow up for patients with diagnosed coeliac disease will be tested in sensitivity analysis.

**Table A4 Costs used in the model**

Costs	Estimate	Range	Source/comment
IgA tTGA	£7.38		Personal communication
IgA EMA	£8.99		Personal communication
IgA tTGA then IgA EMA (subsequent tests and combination tests)	£9.49		Personal communication
Separate IgA	£0.50		Personal communication
Endoscopy biopsy	£410		National Reference costs
Gluten free diet	£180		Prescription cost analysis report, population data, Fowell et al 2006
Cost of follow up for patients diagnosed with coeliac disease (per year)	£100		BSG guidelines, PSSRU 2007, personal communication, assumption

### *Delayed diagnosis*

#### Years to delayed diagnosis

The cost and years to delayed diagnosis has been difficult to estimate within the model. There is evidence that the number of years to diagnosis has fallen in recent years, most

likely due to improved serological testing. Nevertheless this represents an additional cost to the NHS of increased GP visits that are incurred during this time due to undiagnosed coeliac disease. Lo et al (2003) reported an average of 4.4 years and Silano et al (2007) reported an average of 6 years mean duration of symptoms before diagnosis of coeliac disease. Dretzke et al (2004) estimated a diagnostic delay of 5 years for those detected through symptoms based on Corrao et al (2001). Based on this evidence we assumed that patients have a probability of 0.5 per annum of having their disease diagnosed. This translates to all patients who are still alive having their coeliac disease diagnosed within approximately 5 years.

### **Cost of delayed diagnosis**

The cost to the NHS of delayed diagnosis has been difficult to determine. Evidence suggests an increased number of GP consultations as a result of undiagnosed coeliac disease. Cannings-John et al (2007) reported a mean difference between cases and controls of five consultations in the 5 years before diagnosis.

This shows an additional consultation for each year prior to diagnosis. In those with at least one consultation, referrals were also recorded. Details on number of referrals and investigations were also reported. However, only odds ratios were reported making it difficult to estimate resource use with these data. In the base case the cost of delayed diagnosis is equivalent to one additional GP visit per patient per year. This is a conservative estimate and was tested in sensitivity analysis to account for additional costs that may be incurred to referral for further investigations that do not lead to a correct diagnosis.

## **Results**

### **Base case**

In the base case the lowest cost option was the 'no test' strategy. This was also the least effective strategy. This is because no serological test costs will be realised but neither will the benefits of a gluten free diet for patients diagnosed with coeliac disease. There is very little difference in the expected costs or quality adjusted life years (QALYs) between all the serological testing strategies. This is expected as these strategies have similar diagnostic accuracy. The most expensive strategy was to carry out an endoscopy and biopsy on all patients with signs and symptoms. This is due to the

relatively high cost of this procedure in the model. There is very little difference in costs and QALYs between the serological test strategies.

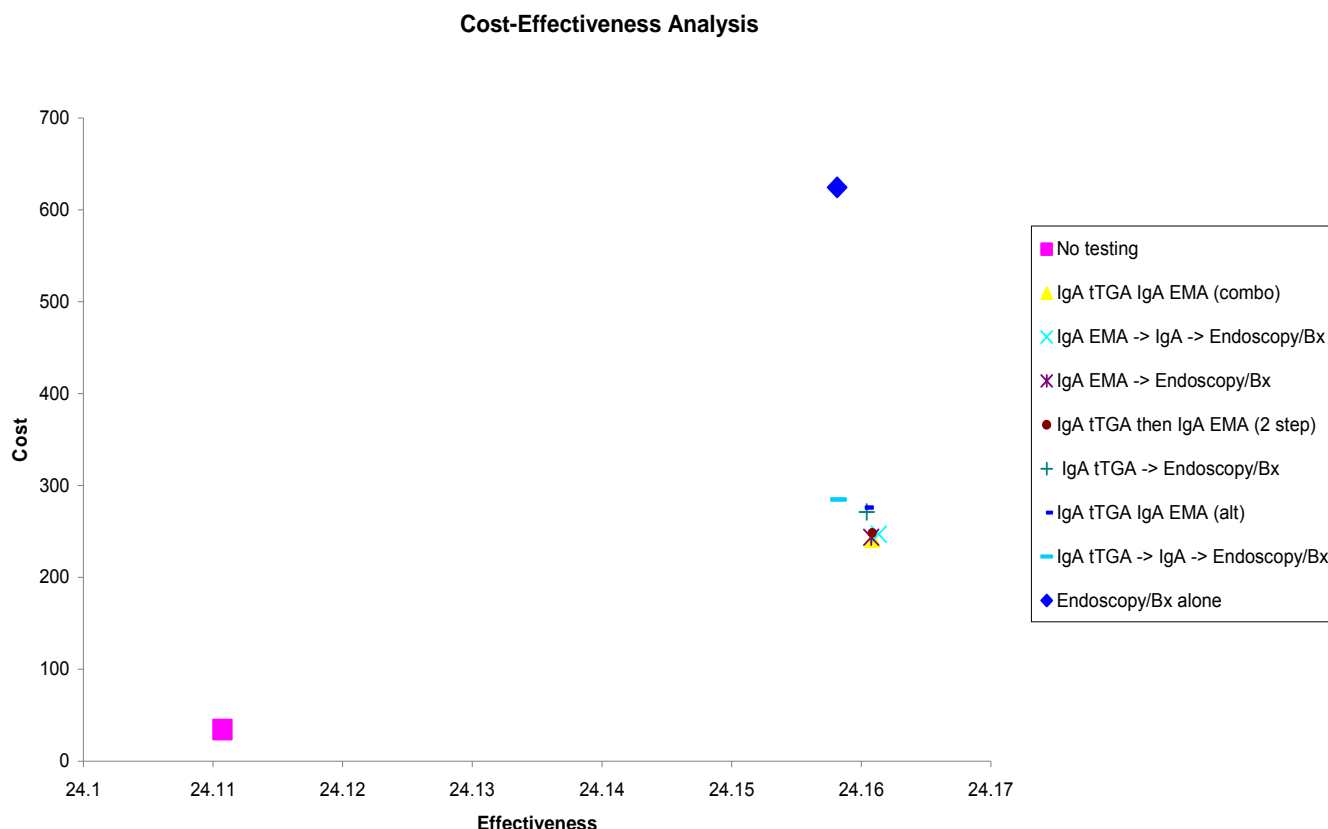
The expected costs and QALYs for each strategy are outlined in table A5 below.

**Table A5 Costs and QALYs for all test strategies**

<b>Strategy</b>	<b>Expected Costs</b>	<b>Expected QALYs</b>
No testing	£34.40	24.1107
IgA tTGA IgA EMA (combo)	£241.50	24.1609
IgA EMA -> Endoscopy/Bx	£243.70	24.1608
IgA EMA -> IgA -> Endoscopy/Bx	£247.10	24.1614
IgA tTGA then IgA EMA (2 step)	£248.30	24.1609
IgA tTGA -> Endoscopy/Bx	£271.10	24.1604
IgA tTGA IgA EMA (alt)	£275.90	24.1603
IgA tTGA -> IgA -> Endoscopy/Bx	£284.60	24.1582
Endoscopy/Bx alone	£624.50	24.1581

Figure A4 shown below shows each of the strategy's costs and QALYs plotted on a graph with cost on the y axis and effectiveness on the x axis. This clearly shows the 'no test' option as the least costly and least effective and shows the serological test strategies all grouped together in the same area showing that they have similar costs and QALYs. The biopsy alone strategy is as effective as the serological test strategies but is more expensive.

**Figure A4 Costs and QALYs of each serological strategy**



The incremental costs and QALYs of each of the strategies compared with the 'no testing' strategy are outlined in table A6 below along with the incremental cost effectiveness ratio (ICER) compared with the 'no testing' strategy.

**Table A6 Costs, QALYs and incremental cost effectiveness ratios for all strategies compared with 'no testing'**

Strategy	Incremental Costs (£)	Incremental QALYs	ICER (£)
IgA tTGA IgA EMA (combo)	£207.10	0.0501	£4134
IgA EMA -> Endoscopy/Bx	£209.30	0.05	£4186
IgA EMA -> IgA -> Endoscopy/Bx	£212.70	0.0506	£4204
IgA tTGA then IgA EMA (2 step)	£214.00	0.0501	£4271
IgA tTGA -> Endoscopy/Bx	£236.70	0.0497	£4763
IgA tTGA IgA EMA (alt)	£241.50	0.0496	£4869
IgA tTGA -> IgA -> Endoscopy/Bx	£250.20	0.0475	£5267
Endoscopy/Bx alone	£590.10	0.0474	£12449

The most cost effective serological test option compared with 'no testing' is to test for both IgA tTGA and IgA EMA on the same sample. This testing strategy costs £4134 per QALY gained and is well within the levels of cost effectiveness according to the NICE methods manual.

All testing strategies are a cost effective option when compared with 'no testing'. Although the endoscopy and biopsy only strategy is also cost effective when compared with 'no testing' it is not cost effective when compared with the other testing strategies and therefore is ruled out.

### **Sensitivity analysis**

#### **Prevalence of coeliac disease**

Due to the uncertainty regarding the prevalence of coeliac disease in the population of interest, a sensitivity analysis was carried out on this variable. The prevalence of 0.0385 was taken from Hopper et al (2008) and was in line with estimates made by other studies in a patient population with an elevated prevalence of coeliac disease (Dretzke et al 2004 and Mein and Ladabaum 2004). When the prevalence of coeliac disease is very low, it is less cost effective to test for coeliac disease in this patient population, however it is still well within the levels of acceptable cost effective interventions. In this scenario the endoscopy and biopsy strategy is no longer cost effective as it may not provide enough benefit to justify the costs of the procedure for all patients. As is expected, the higher the prevalence in this patient population the more cost effective it is to test for coeliac disease. When keeping all other parameters the same and varying the prevalence of coeliac disease to provide an estimate of the effect of uncertainty around the data taken from Hopper et al (2008), this does not significantly affect the results of the model. When the prevalence was varied from 0.00385 and 0.385, representing extreme values, the ICERs for moving from 'no testing' to IgA tTGA and IgA EMA combination testing varied from £6894 to £3859. This shows that the higher the prevalence of coeliac disease in the population the more cost effective it is to use serological testing.

#### **Serological test accuracy**

The data in the model on serological test accuracy were taken from a single study and therefore it is appropriate to carry out sensitivity analysis on these parameters to

establish their influence on the model results. This was carried out using 95% confidence intervals provided in Hopper et al (2008).

In general the model shows that strategies with higher specificity even at the expense of sensitivity are the most cost effective. This is likely to be because more specific tests are accurate at ruling out coeliac disease and avoid the cost of biopsy for positive serological test results.

### **Utilities**

Due to the paucity of evidence on utilities in coeliac disease, extensive sensitivity analysis was carried out on these variables. In the base case, utilities assumed by Dretzke et al (2004) were used. Scenarios using different utility values were explored. In the base case the utilities used assumed a small utility decrement due to untreated coeliac disease compared with treated coeliac disease. There is evidence from the literature that there is a much larger difference between utilities in the untreated and treated health states (Casellas et al 2008). The figures reported in this paper were median values and therefore not as appropriate for use in the economic model, however, as these are the only values in the literature reported using the EQ-5D, they were taken into consideration. When larger differences in utility between untreated and treated coeliac disease are considered in the model, it becomes even more cost effective to implement a testing strategy for people with signs and symptoms of coeliac disease. In this sensitivity analysis the utility of no coeliac disease was set to 1 and data taken from Casellas et al (2008) were used for treated and untreated coeliac disease (0.93 and 0.72 respectively). In this sensitivity analysis, the ICER decreases from £4134 to £1446 per QALY gained. This shows that the greater the benefit gained by treating coeliac disease, the more cost effective the testing strategies become.

The scenario where the utility of treated and untreated coeliac disease is equal, that is, where both treated and untreated coeliac disease is 0.93 was also examined. Although this scenario is less cost effective, it is still within the threshold for cost effectiveness considered by NICE. This is because a small decrement in utility remains between those with coeliac disease and those without. This means that it is cost effective to test for coeliac disease even if there is no difference between treated and untreated coeliac disease. The ICER for combination testing versus 'no testing' when the utility of treated and untreated coeliac disease is equal is £14,862.

One way sensitivity analysis varying the utility of the endoscopy and biopsy did not alter the overall results of the model and only small differences in the ICERs resulted from varying this parameter. This is due to the small effect this disutility has when compared with a lifetime of utility gained by moving from untreated to treated coeliac disease.

### **Mortality**

As there is uncertainty around whether or not coeliac disease affects mortality, sensitivity analysis was carried out around the base case assumptions. These were that there is no difference in mortality between people with treated coeliac disease and the general population. The base case model assumed a decrease in life expectancy of undiagnosed coeliac disease which was also applied to untreated coeliac disease.

The sensitivity analysis was carried out on the SMR for those with untreated and undiagnosed coeliac disease. The lower estimate was 1, that is, people with untreated and undiagnosed coeliac disease have the same mortality as the general population and therefore simulating the scenario where there is no reduction in survival following diagnosis of coeliac disease. Even with this conservative assumption, serological test strategies are cost effective when compared with 'no testing'. This is most likely due to the utility gains made when coeliac disease is correctly diagnosed and treated. The upper estimate was 3 and represented the scenario that those with coeliac disease face a greater increase in mortality compared with the general population than in the base case. Testing becomes even more cost effective in this scenario. The ICER ranged from £5487 to £3502 per QALY gained for combination testing versus 'no testing' when the SMR was varied between 1 and 3.

### **Adherence to a gluten free diet**

There is uncertainty around the number of people who adhere to a gluten free diet. The base case value of 60% of people adhering to a gluten free diet was varied between 30% and 90%. Even at low levels of adherence, serological testing remains cost effective compared with 'no testing'.

## **Costs**

### **Serological tests**

There is uncertainty around the exact costs of serological tests to the NHS. Therefore sensitivity analysis was carried out to establish the effect of varying these costs on the cost effectiveness of the serological test strategies compared with no testing.

The costs of the tests were varied in one way sensitivity analysis. This was carried out by assuming an upper value of the base case cost plus 50% and a lower value of the base case minus 50%.

As expected the cost of the tests do not greatly alter the results of the model. When the costs of the serological tests are lower than the base case value then testing becomes more cost effective. When the serological test costs are higher than in the base case, moving from a 'no test' strategy to a test strategy, results in a higher ICER but remains cost effective.

### **Late detection**

In the base case, 70% of people with false negative results were considered to be correctly identified as having coeliac disease within 5 years. If all people with false negative results are assumed to be untreated in the model this does not significantly alter the results. This is likely to be because there are a very small number of false negatives in the model and therefore changing this variable does not make a substantial difference to the results.

However, the cost of delayed diagnosis is also uncertain and many GDG members felt that costs of additional visits to GPs and additional referrals to secondary care as a result of delayed diagnosis were not often correctly taken into account. Therefore in sensitivity analysis this parameter was varied. As the cost of delayed diagnosis increased, the 'no test' strategy became more expensive and was eventually dominated by (was more costly and less effective than) the serological test strategies. Therefore even at a conservative estimate of the costs associated with delayed diagnosis and untreated coeliac disease, serological test strategies are very cost effective. If the costs of delayed diagnosis are very high, at around £260 per person, it may be cost saving to introduce a serological test strategy, that is, that the 'no test' strategy becomes more costly than the serological test strategies.

### **Probabilistic sensitivity analysis**

Probabilistic sensitivity analysis (PSA) will be added post consultation. The model appears robust when considering one way sensitivity analyses and therefore the overall results are not expected to change. This section of the analysis will allow us to better quantify the level of uncertainty around the input parameters.

## ***Discussion***

### **Evidence limitations**

In general there was good evidence on the diagnostic accuracy of serological tests. There was poor evidence on combination test strategies and therefore only one paper was used to populate the model with sensitivity and specificity data. There was poor evidence on the overall accuracy of strategies including IgA deficiency testing and IgG tTGA and IgG EMA testing. Therefore, in the strategies with IgA deficiency testing, all patients receive an endoscopy biopsy rather than an IgG serological test. It is likely that strategies that include an additional test using IgG prior to biopsy will be more cost effective than strategies without the additional test because fewer endoscopies will have to be carried out.

There was poor evidence on the utility of coeliac disease and untreated coeliac disease. The utility values have the greatest impact on the ICER although even with conservative estimates concerning the difference in utility between treated and untreated coeliac disease the ICER remains well within accepted levels of cost effectiveness.

In general the model appears robust to changes made.

### **Adult and child populations**

It may be that some of the costs included in the model are higher for child populations. For example, the GDG advised that an endoscopy and biopsy may cost more for a child because additional anaesthetic is needed. The sensitivity analysis on parameters such as the cost of endoscopy and biopsy shows that testing for coeliac disease using the strategies outlined in the model is likely to remain cost effective. For this reason separate models for adults and children were felt to be unnecessary.

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## Health economic evidence tables

This section provides evidence tables that summarise the data provided in the published economic evaluations identified for the purpose of this guideline.

Published economic evaluations were quality assessed using methods as described in the current 'Guidelines methods manual' (full details can be found 'The guidelines manual' (2009) by NICE (available from [www.nice.org.uk](http://www.nice.org.uk)).

### Data extraction table for included study

<b>Primary Source</b>	Health Technology Assessment NHS R&D HTA programme	
<b>Author</b>	Dretzke et al 2004	
<b>Date</b>	2004	
<b>Type of economic evaluation</b>	Cost utility analysis	
<b>Currency used</b>	GBP (£)	
<b>Year to which costs apply</b>	2001	
<b>Perspective used</b>	The analysis was from a NHS and PSS perspective.	
<b>Timeframe</b>	Life time dependent on the life expectancy of the population in the model	
<b>Comparators</b>	Various testing strategies were compared in the model: 1. no screening 2. biopsy of all children 3. single autoantibody test confirmed by biopsy in those testing positive 4. combination of autoantibody tests confirmed by biopsy in those testing positive 5. single autoantibody test without confirmatory biopsy 6. combination of autoantibody tests without confirmatory biopsy.	
<b>Source(s) of effectiveness data</b>	The effectiveness data (diagnostic accuracy of the autoantibody tests for coeliac disease) came from the systematic review that was conducted as part of the HTA report.	
<b>Source(s) of resource use data</b>	Resource use data was collected from various sources including published sources and personal communication (for tests)	
<b>Source(s) of unit cost data</b>	Published sources (endoscopy), personal communication (for tests) and BNF (for prescription gluten free products)	
<b>Modelling approach used</b>	Decision analytic model used to quantify life time costs and benefits of screening for coeliac disease at the time of diagnosis for type I diabetes.	
<b>Summary of effectiveness results</b>	Costs and QALYs were not reported separately for each screening strategy. Baseline utilities used in the model were	
	No CD	0.9
	Treated CD	0.88
	Untreated CD	0.82
	Endoscopy	-0.002
	GFD	-0.04
<b>Summary of cost results</b>	<b>Costs (£)</b> – As above, no total costs for the screening strategies were reported.	
<b>Summary of cost-effectiveness results</b>	For the base case (compared with no screening), the lowest cost per QALY gained, was for IgA EMA with confirmatory biopsy, with IgA TTG as the next most cost-effective option with confirmatory biopsy. Combinations of tests were not as cost effective as a single test with confirmatory biopsy. ICERs were as follows IgA EMA = £12,250 per QALY gained IgA TTG = £12,970 per QALY gained The least cost-effective strategy was IgG AGA tests alone or in combination. The biopsy alone strategy was considerably less cost-effective than test plus biopsy confirmation and test alone was less cost-effective than the same test with the addition of the biopsy.	
<b>Sensitivity</b>	One way sensitivity analysis was carried out on many of the parameters in the model, including	

## DRAFT FOR CONSULTATION

<b>analysis</b>	prevalence, sensitivity and specificity of tests, costs, utilities, life-expectancy and discounting. No multiway or probabilistic analysis was carried out.
<b>Main conclusions</b>	The authors state that the decision analytic model indicated that screening for coeliac disease at diagnosis of diabetes was cost effective. In sensitivity analysis, changes in the cost and utility of gluten free diet and utilities of treated and untreated coeliac disease substantially affected the cost effectiveness of the strategies considered.